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Chromium mediated oxidative transposition of secondary benzylic alcohols

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CHROMIUM MEDIATED OXIDATIVE TRANSPOSITION OF SECONDARY BENZYLIC ALCOHOLS

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Master of Science

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ABSTRACT

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Carbonyl transposition serves as an important reaction in organic synthesis. Carbonyl transposition results in transposition of the functional groups without loss of the carbonyl moiety. Chromium oxidations of tertiary unsaturated carbinols have been studied since the 1970's for their ability to cause carbonyl transposition. It is only recently that carbonyl transposition of secondary unsaturated benzylic alcohols has been reported with the use of chromium. Different oxidation reactions were examined for the potential carbonyl transposition products. Oxidation of unsaturated benzylic alcohols were maintained at varying temperature with pyridinium chlorochromate to monitor for the formation of product. As the temperature increased an increase in the benzaldehyde derivative was observed as well as an increase in the transposition product. The electron withdrawing groups gave the lowest yield of the transposed product.

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CHAPTER I

INTRODUCTION

α,β-Unsaturated carbonyls are an important class of organic compounds. The α,β–unsaturated carbonyl consists of a carbonyl (C=O) and an adjacent and conjugated alkene (C=C). Figure 1.1 illustrates how the adjacent alkene is located on the carbons that are alpha and beta to the carbonyl.

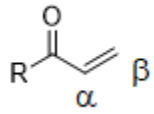


Figure 1.1 α,β-Unsaturated carbonyl

Due to the conjugation, the predominant resonance structure for an α,β–unsaturated carbonyl can be dependent on the characteristics of the other substituents within the system. As illustrated in Figure 1.2, the resonance structures for the conjugated system have a partial positive charge on both the carbonyl carbon and the β–carbon. This indicates the most likely locations for a nucleophile to add to the system in a reaction.

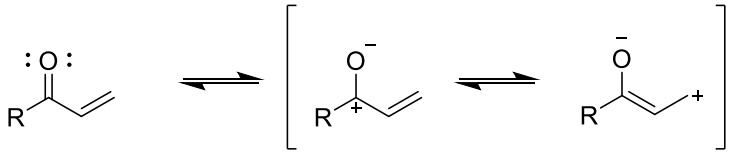


Figure 1.2 Resonance of the alpha beta unsaturated carbonyl

The α,β-unsaturated carbonyl compounds are able to undergo a number of different reactions such as Michael addition, double bond isomerization, radical scavenging, and oxidation/reduction type reactions (Amslinger, 2010). Because the two locations of positive charge are different in terms of their steric requirements and degree of electropositive character, it is possible to selectively target one of the two positions in a nucleophilic attack. In addition, the reaction conditions (solvent, temperature, reagent) can affect the regiochemistry of such a nucleophilic reaction (Deng, Tian, Qu, & Wang, 2002). In some cases, the molecule appears to behave as expected in a reaction. Even when that does happen, the specific reaction can also provide a number of unwanted side products. For example, addition to an α,β-unsaturated carbonyl can occur as a 1,2-addition or as a 1,4-addition (Figure 1.3). Note that the 1,4-addition product can tautomerize readily to the keto-form. This gives the appearance that reaction was a simple alkene addition (Ouellette & Rawn, 2018).

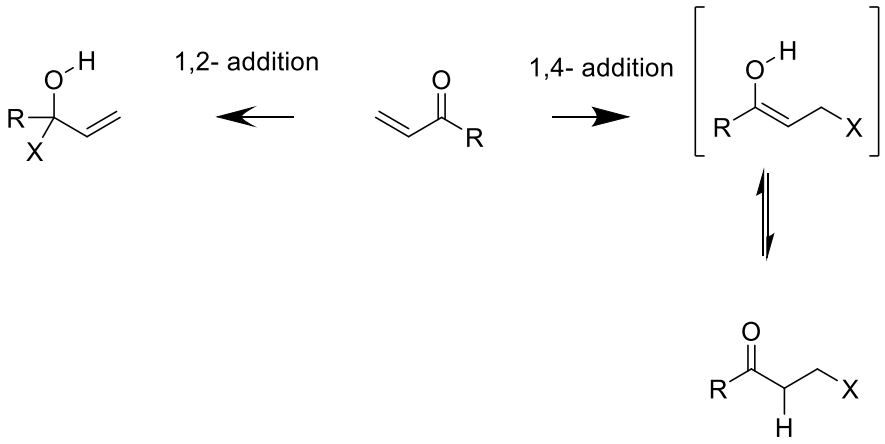


Figure 1.3 Demonstration of nucleophilic addition to an α,β–unsaturated alkene.

The α,β–unsaturated carbonyl system is essential in the biological world. In 2016, Rodrigues and co-workers reported that the α,β–unsaturated carbonyl

functional group is present in one sixth of the known naturally occurring compounds (Rodrigues, Reker, Schneider, & Schneider, 2016). The most widely studied of these naturally occurring α,β−unsaturated carbonyl compounds includes derivatives of curcumin, zerumbone, and the class of chalcones (see Figure 1.4) (Arshad, Jantan, Bukhari, & Hague, 2017).

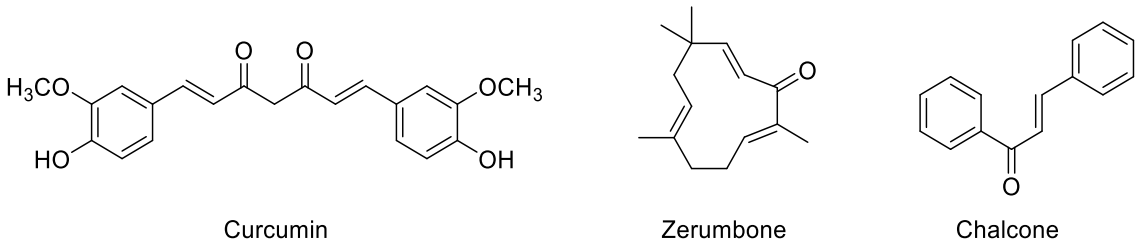


Figure 1.4 α,β−Unsaturated carbonyls occur in many naturally occurring compounds

α,β−Unsaturated carbonyls are also found to be part of the backbone of many corticosteroids as seen in Figure 1.5. Corticosteroids are an important class of steroids secreted by the adrenal cortex that are responsible for the regulation of a number of biological functions (Manickam, Arizaleta, Gurusamy, & Bhansali, 2017).

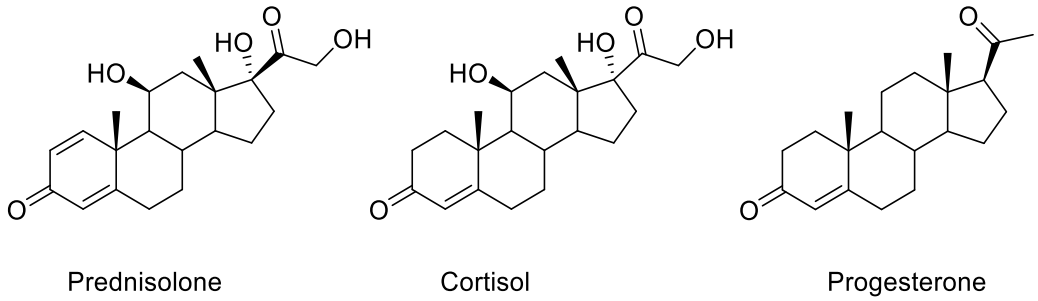


Figure 1.5 α,β−Unsaturated steroids

The carbonyl group of the α,β-unsaturated ketone can appear to migrate during its formation via oxidation of an α,β-unsaturated carbinol. This process is

known as oxidative carbonyl transposition. This transposition can produce a number of new reactions from the same starting material as shown in Figure 1.6. This reaction could be a useful route to a number of pharmaceutically useful products that utilize an α,β–unsaturated carbonyl intermediate.

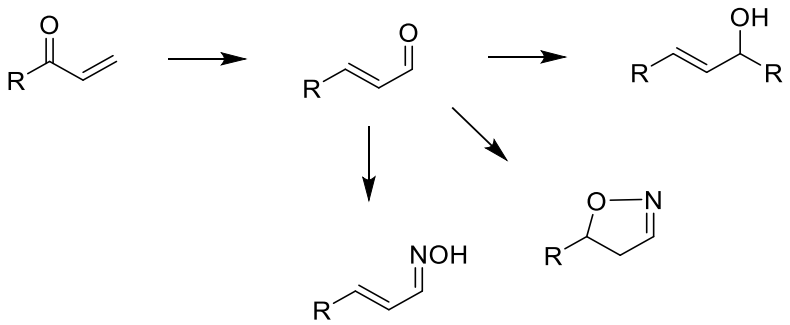


Figure 1.6 Selected potential products resulting from carbonyl transposition

To explore the utility of a terminal α,β–unsaturated system that undergoes carbonyl transposition, we were interested in exploring the oxidation of a series of α,β–unsaturated carbinols. Using a set of common oxidizers, the product mixture that resulted could be evaluated as a function of time, temperature and substituent electronic character. Figure 1.7 illustrates the overall planned reaction scheme and the proposed products that are anticipated to result from the oxidation. The effect of each modification to the reaction will be correlated to the product distribution.

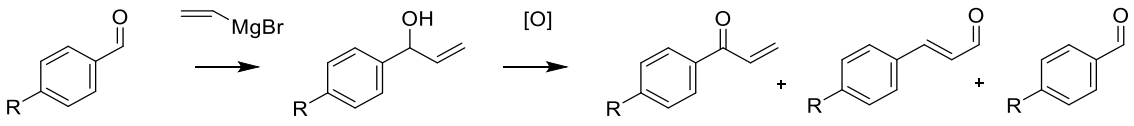


Figure 1.7 Oxidation of an unsaturated alcohol to yield a mixture of carbonyl transposition products.

CHAPTER II

LITERATURE REVIEW

Oxidation

Oxidation can be defined as the loss of electrons or the decrease in number of bonds to hydrogen atoms. The oxidation of a compound in a reaction requires a concurrent reduction during the reaction. The species that loses the electrons is said to be oxidized while the species that gains electrons is reduced. Oxidation is also seen as an increase in the number of bonds to oxygen or another electronegative atom. In organic chemistry, a common oxidation pathway involves the conversion of a primary alcohol to an aldehyde and then to the carboxylic acid (Figure 2.1).

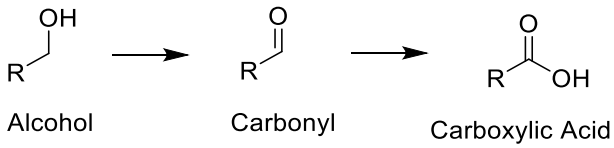


Figure 2.1 Oxidation of alcohol to carbonyl and carboxylic acid

Oxidizing agents range in strength (or oxidizing ability), toxicity, as well as reaction times and potential side reactions. There are a number of common oxidizing agents in organic chemistry including sodium hypochlorite, nickel peroxide, and manganese dioxide.

Sodium hypochlorite, NaOCl, is a common oxidizing agent used alone to oxidize another compound and also as a co-oxidant or secondary oxidizing

agent. It is commercially available in a product known as ‘bleach’, sold generally as a ~5.0% m/v solution of NaOCl. It is also available in powdered form from chemical companies (Grill, Ogle, & Miller 2006).

Sodium hypochlorite was used as a co-oxidant with nickel(II) salts as an oxidizing agent by Grill and group in 2006. The original scope of the oxidative research examined the formation of epoxides. The double bond of the α,β–unsaturated carboxylic acids is easily oxidized to form the epoxide functional group. Grill and co-workers also discovered that the oxidation of 3-butenoic acid gave a significant amount of fumaric acid (77% yield). This product resulted from the oxidation of an allylic C-H bond. The overall reaction can be seen in Figure 2.2 (Grill, Ogle, & Miller 2006).

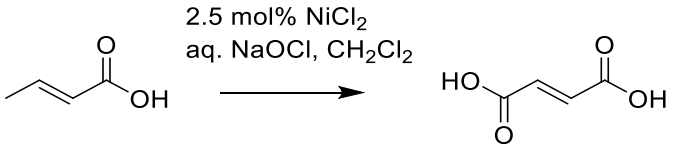


Figure 2.2 Oxidation of 3 butenoic acid to fumaric acid

Alinezhad and group in 2009, used sodium hypochlorite in a silica gel system as an oxidizing agent for benzylic and allylic alcohols. The reactions proceeded rapidly and in high yields for primary alcohols. The benzylic oxidation ranged from 5 minutes to 80 minutes and gave yields that ranged from 65-98 % when oxidizing primary alcohols as seen in Figure 2.3. The yield decreased drastically when a secondary alcohol was used in place of the primary alcohol. The oxidation of the secondary alcohols such as phenylalcohol resulted in yield of only 30% acetophenone after 70 minutes (Alinezhad, Tajbakhsh, & Soleimani, 2009).

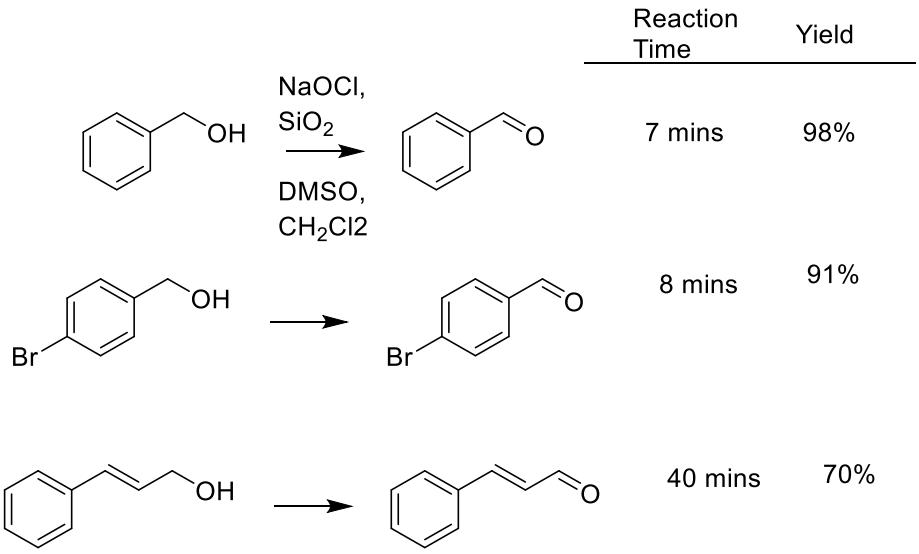


Figure 2.3 Oxidation of benzylic and allylic alcohols using a NaOCl and SiO_2

Manganese(IV) oxide (MnO_2, also known as manganese dioxide) is well suited for the preparation of unsaturated ketones via the oxidation of secondary allylic alcohols (Highet & Wildman, 1955). Manganese dioxide has also been used in the oxidation of vitamin A to retinene (Figure 2.4) as well as the oxidation of other unsaturated allylic alcohols (Henbest, Jones, & Owen, 1957).

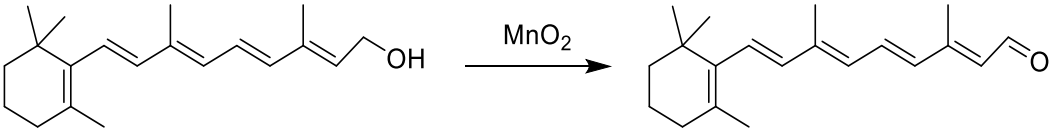
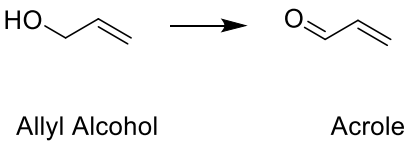


Figure 2.4 Oxidation product retinene from MnO_2 oxidaiton of Vitamin A

Bond cleavage products have been reported with the use of manganese dioxide in oxidations to obtain ketones. The cleavage product is formed via a free radical mechanism. Gritter and Wallace discovered in 1959, that saturated secondary alcohols react slower than aryl carbinols. They reported the oxidation of allylic alcohols using a range of different solvents. Petroleum ether was found to result in the highest yield of oxidation products when compared to chloroform

and carbon tetrachloride. Gritter and Wallace also explored the reaction of allyl alcohol with different manganese salts. The group found that preparation of the manganese dioxides from manganese chromate ($MnCrO_4$) and permanganates resulted in the fastest reactions with the highest yields. It is likely that residual manganese chromate or permanganate complexes precipitated with the desired manganese dioxides. The complexes may have had an effect on the yield of the reaction (Figure 2.5) (Gritter & Wallace, 1959).

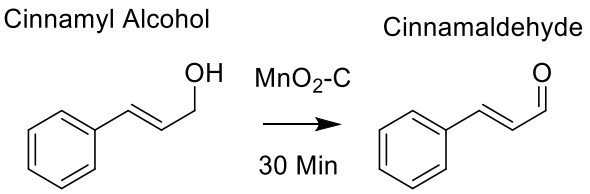


Allyl Alcohol Acrolein

MnO_2 prepared from	Yield (%)	Time (hrs)
$MnCrO_4$	95	29
$Ba(MnO_4)_2$	70	24
$Mn(OAc)_2$	92	57

Figure 2.5 The reaction time and yield of the oxidation of allyl alcohol varies with the manganese salt used in preparation of MnO_2

In 1970, Carpino found that a reactive form of manganese dioxide could be precipitated onto charcoal. The MnO_2-C was then either dried by air or oven. The performance of the oxidizer in the conversion of trans-cinnamyl alcohol to trans-cinnamaldehyde was evaluated. The percentage of cinnamaldehyde present in the end sample was determined via an infrared spectroscopic analysis. Carpino found the greatest conversion to cinnamaldehyde occurred when the MnO_2-C was precipitated at room temperature and dried in the oven (Figure 2.6) (Carpino, 1970).



Condition	%Cinnamaldehyde
Air Dried, bp	30-35
Oven Dried, bp	46-51
Air Dried r.t	48-54
Oven Dried r.t.	82-91

Figure 2.6 Conversion of unsaturated primary alcohol into unsaturated carbonyl compound through the use of Manganese dioxide

In 1997, Aoyama and co-workers examined the use of manganese dioxide on the oxidation of benzylic and allylic alcohols (Figure 2.7). Oxidation of trans-cinnamyl alcohol resulted in conversion to trans-cinnamaldehyde with a yield of 88%. The oxidation of other secondary allylic alcohols gave yields of 85 %. The group reported that isomerization was not observed in the oxidation of alcohols with cis- or trans-alkenes (Aoyama, et al., 1998).

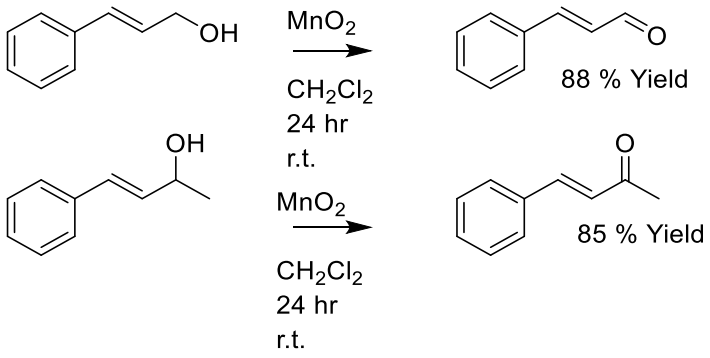
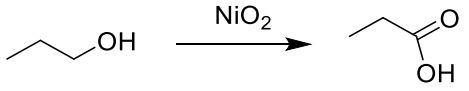


Figure 2.7 Oxidation of benzylic and allylic alcohols

Nickel(IV) oxide (also known as nickel peroxide) was reported as an oxidizing agent in 1962 by Nakagawa and co-workers (Nakagawa, Konaka, & Nakata, 1962). This compound can be easily prepared by mixing nickel(II) sulfate with aqueous sodium hypochlorite. Nickel peroxide is believed to be a better oxidizing agent than manganese dioxide as the same oxidation can occur using much smaller quantities of the oxidizer (George & Balachandran, 1974). Nickel

peroxide was shown to be a good oxidizing agent for converting primary alcohols into carboxylic acids and secondary alcohols into carbonyls. Some of their key findings are shown in Figure 2.8 (Nakagawa, et al., 1962).



	Time (hr)	
Alcohol	0.5	1
EtOH		96.6
n-PrOH		74.9
n-BuOH		81.6
i-BuOH	47.8	59.1
*i-BuOH	19.6	20.1

Figure 2.8 Yields of carboxylic acids from primary and secondary alcohols with 1.5 equivalents nickel peroxide at 30 °C (*indicates reaction was held at 0 °C)

Nakagawa and co-workers examined the oxidation of a number of alcohols containing an aromatic ring system. For example, trans-cinnamyl alcohol was oxidized to the corresponding trans-cinnamic acid in 81 % yield when the reaction was heated to 50 °C for 6 hours in an alkaline solution containing 0.5 M sodium hydroxide. The oxidation of some substituted benzylic alcohols with nickel peroxide resulted in an over oxidation product. This was observed in the case of both para- and meta-methyl substituted benzylic alcohols as seen in Figure 2.9.

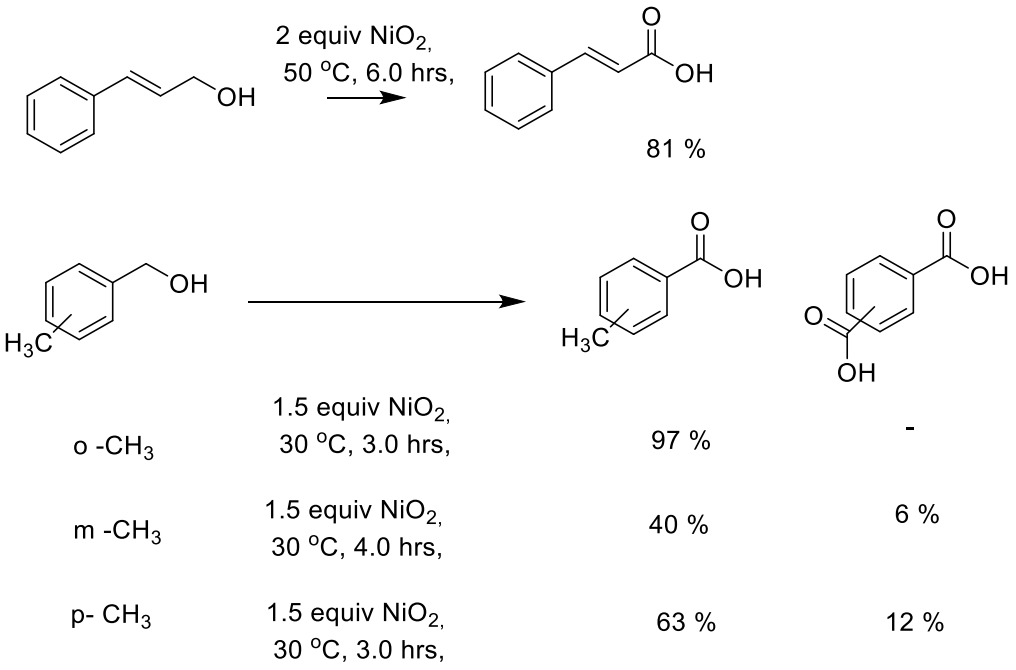


Figure 2.9 Oxidation of aromatic alcohols using nickel peroxide

Some allyl alcohols have been shown to undergo an oxidative cleavage with nickel peroxide. For example, oxidation of 3-phenyl-1-propanol favored the formation of the expected 3-phenyl-1-propanoic acid at lower temperature and shorter reaction times. However, the quantity of the cleavage product (benzoic acid) was increased as the temperature and time of the oxidation increased (Figure 2.10) (Nakagawa, et al., 1962).

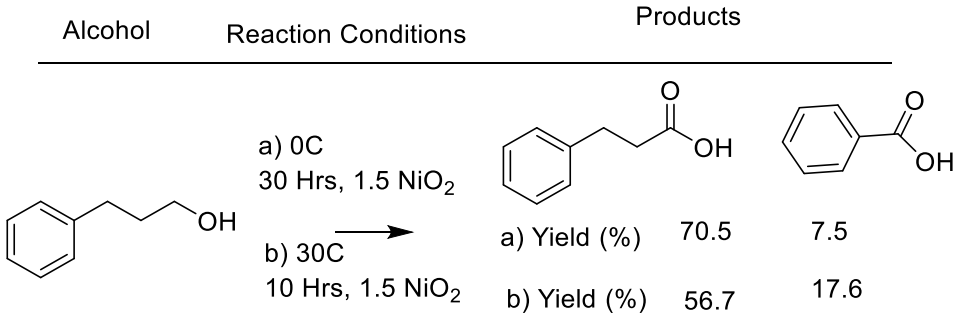


Figure 2.10 Oxidation of 3-phenyl-1-propanol

The oxidation reaction using nickel peroxide was studied by Konaka and coworkers in 1969 using electron spin resonance spectroscopy. From their data, they were able to propose a radical mechanism for the nickel peroxide oxidation (Figure 2.11). Oxidation of benzyhydrol-^{18}O with 0.5 equivalents NiO_2 resulted in an oxidation product in which ^{18}O was maintained on the benzophenone. Based on the retention of the ^{18}O, the actual oxidation procedure likely involved pathway B in which the oxidation takes place on the surface of the metal (Konaka, Terabe, & Kuruma, 1969).

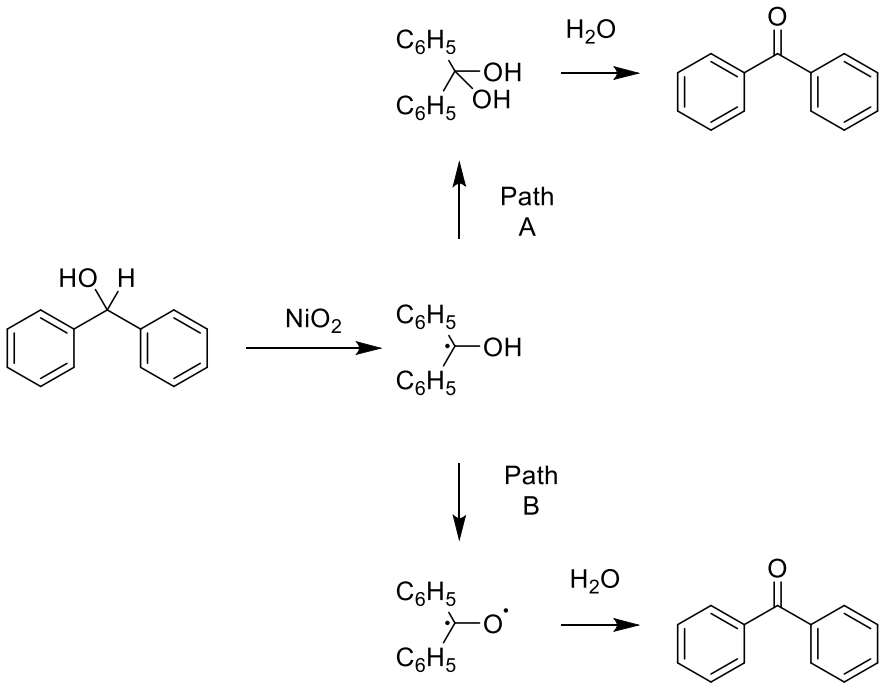


Figure 2.11 Free radical cleavage during nickel peroxide oxidation

In 1978, Firouzabadi and Ghaderi reported the use of barium permanganate ($Ba(MnO_4)_2$) as an oxidizing agent in organic reactions. The $Ba(MnO_4)_2$ was prepared by the addition of 1.0 equivalent barium chloride, 1.0 equivalent potassium permanganate, 1 equivalent sodium hydroxide, and 0.12 equivalent potassium iodide in water. The reaction was heated and the

$Ba(MnO_4)_2$ was collected via suction filtration and then dried in desiccator prior to its use in oxidation reactions. The reactions were carried out in dichloromethane and gave yields that ranged from 80-95 %. Figure 2.12 gives an example of two of the aromatic carbinols that where oxidized. The oxidation of benzhydrol gave the expected ketone benzophenone in a 95 % yield after 4 hours. The oxidation of the dicarbinol naphthalene gave the expected ketone after 12 hours in an 87 % yield. When more polar solvents were used, the reaction times increased for the alcohols tested, the extraction process was also more difficult (Firouzabadi & Ghaderi, 1978).

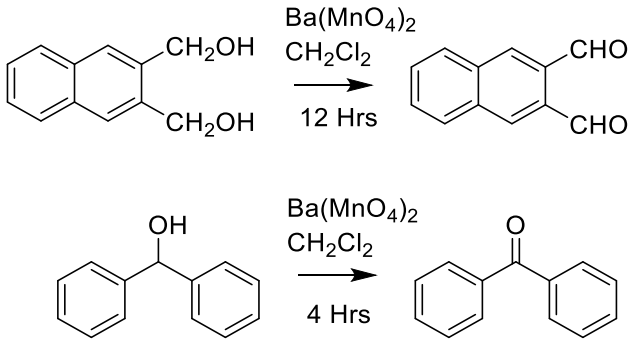


Figure 2.12 Oxidation of allylic alcohols with barium manganate in dichloromethane at room temperature.

Hydrogen peroxide (H_2O_2) as an oxidizing agent has the advantage of being less toxic then many of the metal oxidizing agents. In 2012, Nishida and Hayashi reported on the oxidation of 9-fluorenol into 9- fluorenone with the use of hydrogen peroxide in xylene on activated carbon as seen in Figure 2.13. By varying the equivalents of H_2O_2 the group was able to determine how yield changes with oxidizing equivalents. The group found that 10 equivalents of hydrogen peroxide showed the highest yield of 77 %. However, when increased

to 15 equivalents peroxide the yield of ketone dropped to 35 % (Nishida & Hayashi, 2012).

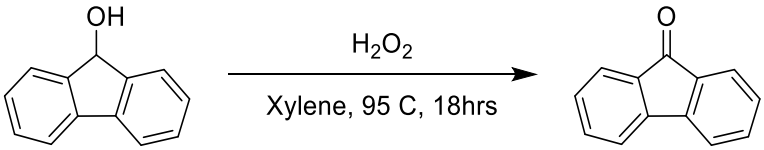
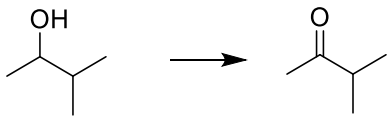


Figure 2.13 Oxidation to 9-flourenone with hydrogen peroxide

Chromium(VI) Oxidizing Agents

Chromium salts have been studied as oxidizing agents since the 1940's. Chromium(VI) oxidizing agents that have been quite successful in providing adequate yields of expected products include pyridinium chlorochromate (PCC) (Corey & Suggs, 1975), pyridinium dichromate (PDC) (Corey & Schmidt, 1979), the Jones' reagent (H_2CrO_4 in acetone) (Bowden, Heilbron, Jones, & Weedon, 1946) and the Fieser reagent (CrO_3 in acetic acid) as well as others (Kiloran et al., 2016).

In 1961, Brown and Garg studied the oxidation of secondary alcohols. Their reagent consisted of a solution of chromic acid (formed from sodium dichromate dihydrate and sulfuric acid) that was added over 15 minutes to a solution of their alcohol in diethyl ether. This process allowed for the formation of an immiscible organic layer that would extract any ketones formed during the reaction and protect them from further oxidation. The oxidation of secondary alcohols occurred cleanly without epimerization. Gas chromatography (GC) was used to determine the purity and yield of the oxidation. The yield of ketone product ranged from 85-97% (Brown & Garg, 1961) (Figure 2.14).



Alcohol	G.C Yield (%)
3-Methyl-2-butanol	85
Cyclopentanol	87
Cyclohexanol	92
Cyclooctanol	93
2-methylcyclohexanol	97

Figure 2.14 Chromium oxidation of secondary alcohols in ether

Brown and co-workers reported the best solvent employed for the oxidation of secondary alcohols was diethyl ether. The group examined reaction times and temperature during the oxidations of simple alcohols such as cyclohexanol, cyclopentanol, and 3-methyl-2-butanol showing that the reactions at room temperature were more favorable than those of lower temperatures (Brown, Garg, & Lio, 1971).

Brown and co-workers studied the oxidative of secondary alcohols with chromic acid and the potential for bond cleavage products. Figure 2.15 illustrates the process that they proposed for the oxidation of secondary alcohols with chromic acid. The oxidation of secondary alcohols with Cr(V) is believed to occur at a quicker rate to yield Cr(III). The rate limiting step is believed to be the oxidation of the secondary alcohol to yield Cr(VI). Chromium(V) is then formed by the exchanges of electrons for Cr(IV) to give Cr(VI) (Brown et al. 1971).

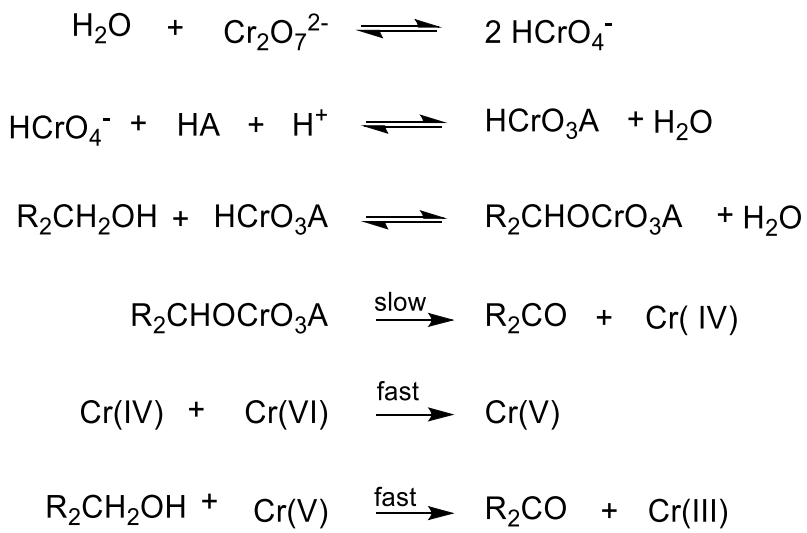


Figure 2.15 Oxidation of secondary alcohols with chromic acid

The group confirmed that either Cr(IV) or Cr(V) may be responsible for the oxidative cleavage observed in some tertiary alcohols such as that seen in Figure 2.16. Their work also illustrated that ketone yield could be reduced by decreasing the temperature or by decreasing the reaction time (Brown et al. 1971).

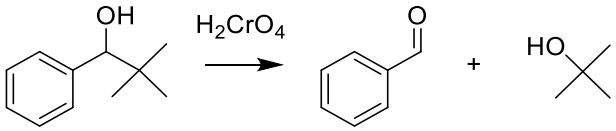
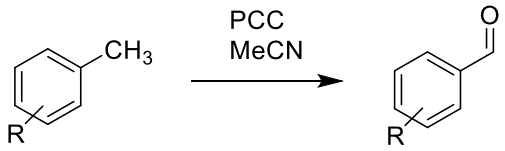


Figure 2.16 Oxidative cleavage of benzylic alcohols with chromic acid

As an oxidizing agent, PCC is slightly acidic and oxidizes products cleanly under mild reaction conditions. For example, at room temperature, PCC can oxidize primary and secondary alcohols to aldehydes and ketones, respectively, without the risk of formation of the carboxylic acid. However, PCC is not recommended for the oxidation of molecules containing sensitive functional groups due to the slight acidity of the oxidizing agent (Fernandes & Kumar, 2002).

In 2005 Hosseinzadeh and group reported on the selective oxidation of methylarenes with PCC. The oxidation of the methylarenes where completed under reflux with acetonitrile and 1 equivalent PCC per equivalent alcohol. The reaction times varied for the methylarenes substituents test. The group demonstrated that the activating methylarenes led to the highest yield of oxidized product and the deactivating group prevents the reaction (Figure 2.17). Over oxidation to the carboxylic byproduct was not observed (Hosseinzadeh, Tajbakhsh, & Vahedi, 2005).



R	Time	Yield (%)
p-NO_2	18	-
o-Br	8	10
p-OCH_3	2.5	82
H	3	89
p-CH_3	2	78

Figure 2.17 Oxidation of methylarenes with PCC under reflux.

In 2002, Fernandes and Kumar investigated the oxidation of homobenzylic alcohols with PCC. Figure 2.18 demonstrates the oxidative carbon-carbon bond breaking potential of PCC seen through the loss of 1 carbon unit. An 8-hour oxidation maintained at room temperature of 2-(4-benzyloxyphenyl)ethanol with 1.5 equivalents PCC resulted in a 1:3 production of the expected 2-(4-benzyloxyphenyl)-acetaldehyde and 4-benzyloxybenzaldehyde. When the concentration of PCC was increased to 3 equivalents the benzaldehyde derivative was obtained as the sole product (Fernandes & Kumar, 2003).

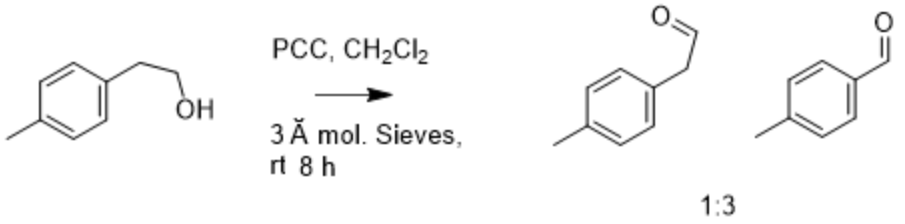


Figure 2.18 Oxidative cleavage resulting in loss of one carbon unit.

In 1968, Rocek & Radkowsky proposed a mechanism for the oxidative bond opening that occurs during the oxidation of cyclobutanol with chromium(IV) as seen in Figure 2.19. The mechanism proposed for the chromium carbon-carbon oxidative cleavage was based on a previously established mechanism that examined the oxidation reduction of a system with both vanadium and chromium of different oxidation states.

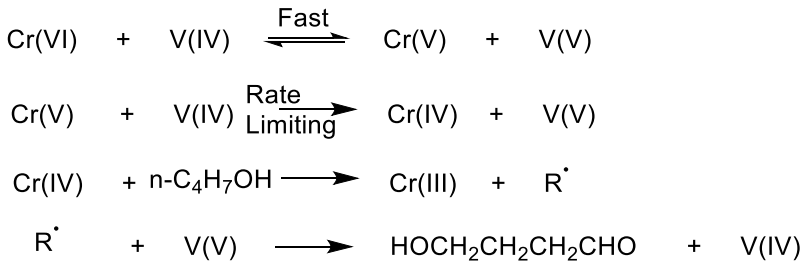


Figure 2.19 Chromium- Vanadium oxidation. R^{*} stands for free radical.

The group demonstrated that Cr(V) was relatively unreactive with cyclobutanol and that the reduced Cr(IV) was much more reactive with cyclobutanol and competes with that of V(IV). The oxidative bond cleavage was proposed to be the result of chromium (IV) or (VI) which acts as a catalyst involved in the carbon-carbon cleavage of cyclobutanol (Rocek & Radkowsky, 1968).

Oxidative cleavage of allylic alcohols has been seen previously by Norman and group in 2007, with a 1-10 % formation of the aldehyde derivative in the oxidation of a beta unsaturated carbinols with PCC as seen in Figure 2.20. The oxidative cleavage product was observed in all of the reactions. It was postulated that the aromatic aldehyde was the result of a Cope-type rearrangement occurring during oxidation (Norman, Shurrush, Calleroz, & Mosher, 2007).

Figure 2.20 Oxidation of benzylic alcohols resulted in the oxidative benzaldehyde derivative

An oxidant related to PCC is PDC. This salt has the advantage of being better for the oxidation of molecules that are acid-sensitive This oxidizer PDC differs from PCC in that it can oxidize primary alcohols to aldehydes in dichloromethane, but in dimethylformamide (DMF) primary alcohols are oxidized to their corresponding carboxylic acids. Corey and Schmidt demonstrated in 1979 how a 50% excess of PDC afforded allylic ketones in good yield after 9 hours in dichloromethane at room temperature as seen in Figure 2.21 (Corey & Schmidt, 1979).

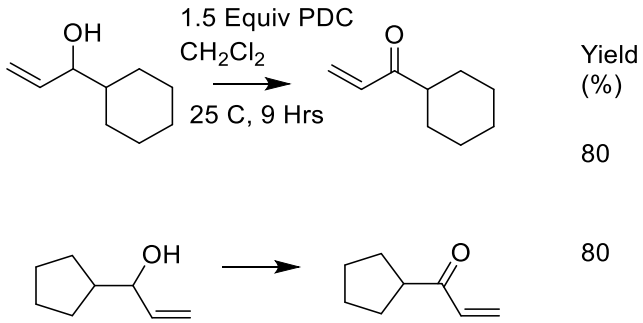


Figure 2. 21 Oxidation of allylic alcohols with the use of PDC in dichloromethane.

Czernecki, Vijakumaran, and Ville in 1986, reported the use of PDC in ethyl acetate as an effective way to oxidize allylic alcohols. Figure 2.22 gives an example of the oxidation of glycals. The oxidation of differing glycals with PDC gave yields that ranged from 40-94%. This was comparable to the yields of other known oxidative procedures of the time (Czernecki, Vijakumaran, & Ville, 1986).

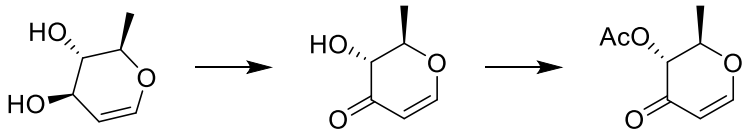


Figure 2.22 Oxidation of glycals

Chromium has been used as a catalyst in the oxidation of cholesteryl acetate with t-butyl hydroperoxide (t-BuOOH). The chromium catalyzed allylic oxidation resulted in the formation of the 7-keto-Δ^5-steroids and a mixture of α- and β-epoxides from the Δ^5-steroids as seen in Figure 2.23. The reaction was performed in varying solvents, over different reaction times, and at different concentrations of t-BuOOH. The chromium(VI) catalyst PCC, PDC, and CrO_3 were all examined for their oxidative effects on the reaction. Use of PCC resulted in formation of only trace amounts of epoxide yield but with also a low conversion and yield (Fousteris, Koutsourea, Nikolaropoulos, Riahi, & Muzart, 2006).

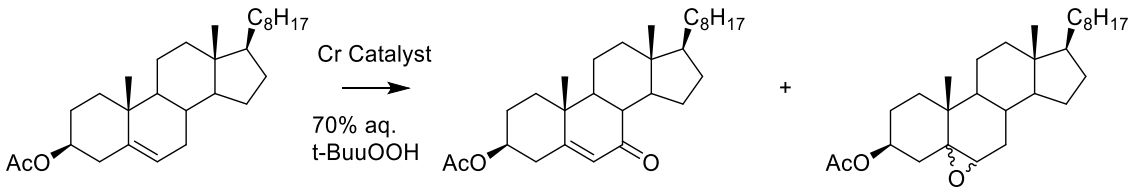


Figure 2.23 Chromium catalyzed oxidation of Δ^5-steroids

Carbonyl Transposition

Carbonyl transposition is the process of transferring a carbonyl group to another position within the molecule. The carbonyl transposition can occur independently or alongside either transposition or loss of another functional group. Much of the work around carbonyl transposition employs the use of a chromium(VI) (Luzzio, 2012).

An early example of carbonyl transposition was reported in 1921 when Lankshear and Perkin developed a synthesis to obtain epicamphor during their synthesis of camphor. This transformation involved a 1,2-carbonyl transposition as seen in Figure 2.24 (Lankshear & Perkin, 1921).

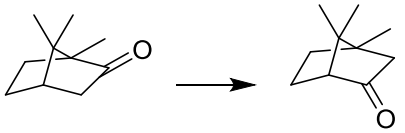


Figure 2.24 Lankshear and Perkin demonstrated 1,2-carbonyl transposition in the preparation of epicamphor

1,3-Carbonyl transposition is generally seen when an alkene shift occurs alongside a carbonyl transposition. Much of the work in the 1970s and 1980s focused around carbonyl transposition during a carbon-carbon bond forming reaction, such as that of a lithium or Grignard addition to an unsaturated ketone, and the subsequent oxidation of the alcohol. Chromium salts were used as the primary oxidant to oxidize the tertiary alcohol. This compound then undergoes

rearrangement with the alkene giving rise to the 1,3-carbonyl transposition as seen in Figure 2.25.

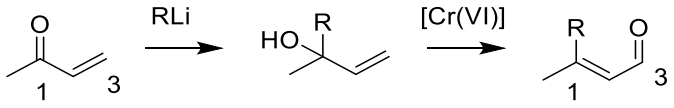


Figure 2.25 Demonstration of a common form of 1,3-carbonyl transposition

Büchi and Egger in 1971, reported on a synthesis in which oxidation of an alcohol with chromium trioxide gave rise to jasmone. The carbinol was prepared via methyl lithium addition to a dienone. The overall reaction resulted in a 90% yield of jasmone from the dienone. The oxidation involved a carbonyl transposition as shown in Figure 2.26. The reaction took place on a 0.75 mmol scale for the starting ketone (Büchi & Egger, 1971).

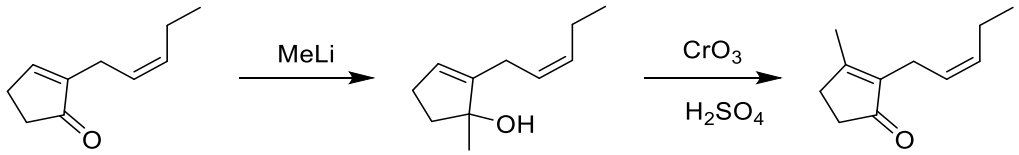


Figure 2.26 Demonstration of carbonyl transposition in carbinol oxidation to obtain Jasmone.

The oxidation of an unsaturated tertiary alcohol with PCC to produce carbonyl transposition is known as the Babler oxidation (Babler & Coghlan, 1976) A year later in 1977, Dauben and Michno demonstrated the transposition in cyclic compounds as seen in Figure 2.27 (Dauben & Michno, 1977). The reaction has been referred to as the Babler-Dauben oxidation (Kiloran, Rossington, Wilkinson, & Hadfield, 2016) although oxidative rearrangement of tertiary alcohols employing the use of chromium(VI) was demonstrated by Bűchi and Egger in 1971 as previously discussed.

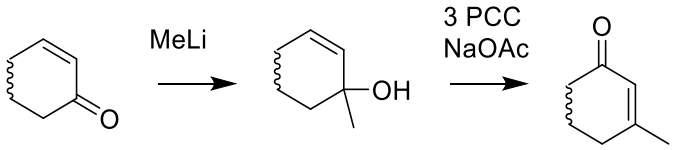


Figure 2.27 Dauben and Michno demonstrated 1,3- carbonyl transposition in cyclic systems (Dauben & Michno, 1977)

In 1993, Nangia and Rao reported on the 1,3-oxidative carbonyl transposition of dihydro-γ-pyranose into dihydro-α-pyranose. The group prepared the dihydro-γ-pyranose by treatment of the hydroxy-butanones with 2 equivalents tin(IV) chloride and triethoxymethane. An alkyl lithium addition to the carbonyl afforded the tertiary alcohols. Oxidative transposition of the tertiary alcohols was accomplished with the use of 1.5 equivalents PCC in dichloromethane. The product dihydro-α-pyranose had yields that ranged from 69-77 % (Nangia & Rao, 1993).

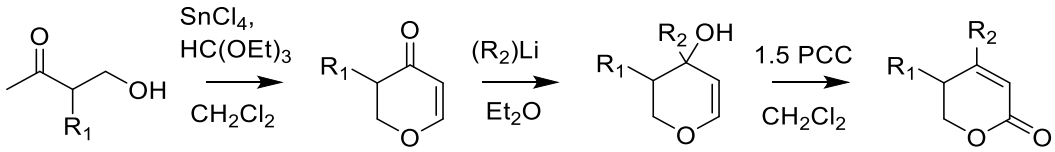


Figure 2.28 Carbonyl transposition in the synthesis of dihydro-α-pyranose

Carbonyl transposition has been demonstrated using a variety of oxidizing agents. Shibuya, Tomizawa, and Iwabuchi in 2008, demonstrated the carbonyl oxidative rearrangement of tertiary alcohols with the use of dichloromethane and 1.5 equivalent oxoammonium salt. Both SbF_6 and BF_4 were successful in causing the oxidative carbonyl transposition. The oxidations resulted in yields of 95 % and 97 % respectively. An example of this oxidative rearrangement is shown in Figure 2.29 (Shibuya, Tomizawa, & Iwabuchi, 2008).

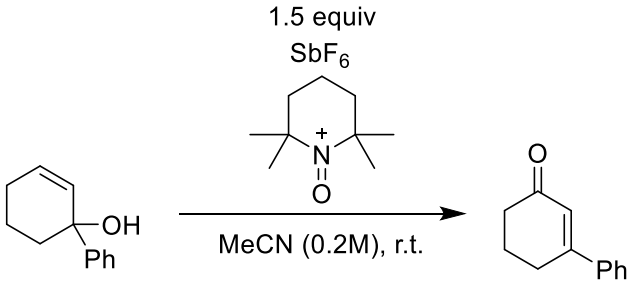


Figure 2.29 Oxidative rearrangement with the use of oxoammonium salts

In 2008, Khurana and group reported on a three-step method for the 1,3-carbonyl transposition of chalcones. The first step was done through a nickel(II) chloride reduction involving $NaBH_4$ to yield the secondary benzylic alcohol. Next, a thermal dehydration was completed in a Dean-Stark apparatus using refluxing benzene. The dehydration resulted in yields ranging from 83-95 %. Oxidation for 24 hours under reflux with selenium dioxide in ethanol afforded the desired para-substituted chalcones with oxidative yield that ranged from 50- 58 % (Khurana, Dawra, & Majumdar, 2008).

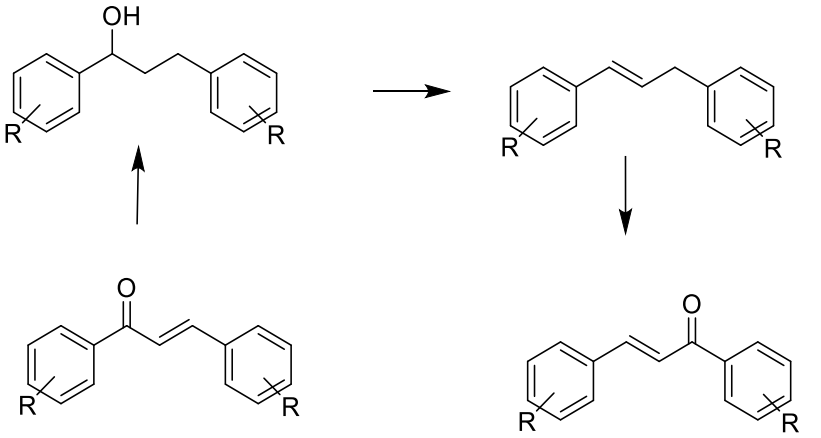
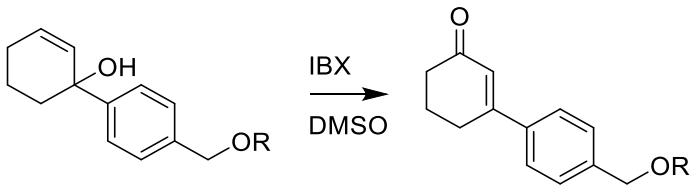


Figure 2.30 A three-step reaction affords the desired 1,3-allylic carbonyl transposition

Shibuya and co-workers examined the oxidative transposition of tertiary alcohols with an iodine(V) reagent. The group used 1-hydroxy-1,2-benziodoxal-

3(1H)-one-1-oxide (IBX) in DMSO to selectively oxidize a variety of tertiary alcohols. The group ran the reaction with a variety of common protecting groups such as acetyl (Ac), methoxymethyl ether (MOM), and tert-butyldiphenylsilyl (TBDPS). Transposition of the tertiary alcohol proceeded in high yields without affecting the protected alcohol as seen in Figure 2.31 (Shibuya, Ito, Takahashi, & Iwabuchi, 2004).



R	Yield (%)
Ac	81
MOM	88
TBDPS	82

Figure 2.31 Oxidative rearrangement with Iodine(V) reagent

In 2016, it was demonstrated by Killoran and group that the carbonyl transposition of secondary alcohols may occur during the oxidation of allylic benzylic alcohols. The compound undergoes a 1,3-carbonyl transposition through the use of catalytic chromium containing periodic acid as a co-oxidant. The reaction required the use of acetonitrile. The group was successful in the transposition of a variety of functional groups, however alkyl substituted secondary alcohols did not result in the oxidative transposition product (Kiloran et al, 2016).

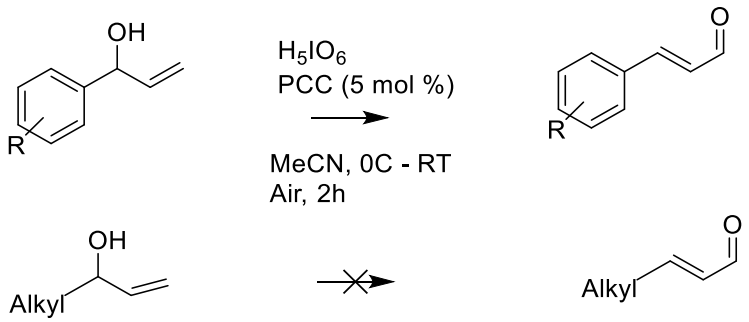


Figure 2.32 Reaction by Killoran et al. demonstrating the carbonyl transposition of aryl alcohols

Killoran and group proposed two potential mechanisms for the formation of (E)- cinnamaldehyde as seen in Figure 2.33. Pathway A demonstrates the formation of a carbocation intermediate. The addition of the chromium back on to the carbocation in a transposed location generate the alkene (E)-cinnamaldehye. The other proposed mechanism was that of pathway B, a 3,3-sigma tropic rearrangement. (Kiloran et al., 2016). The group proposed the carbocation intermediate, Path A, as the predominant pathway due to the acidic nature of the reaction mixture and the necessity of an aryl group alpha to the secondary alcohol (Kiloran et al., 2016) (as seen above in Figure 2.33). However, most sigmatropic rearrangements are done in the presence of heat to drive the formation of the rearranged product. It is possible that added heat is unnecessary for the aryl carbonyl-alkene rearrangement due to the driving force of obtaining conjugation of the aryl ring system and for the formation of the end product that is thermodynamically more stable.

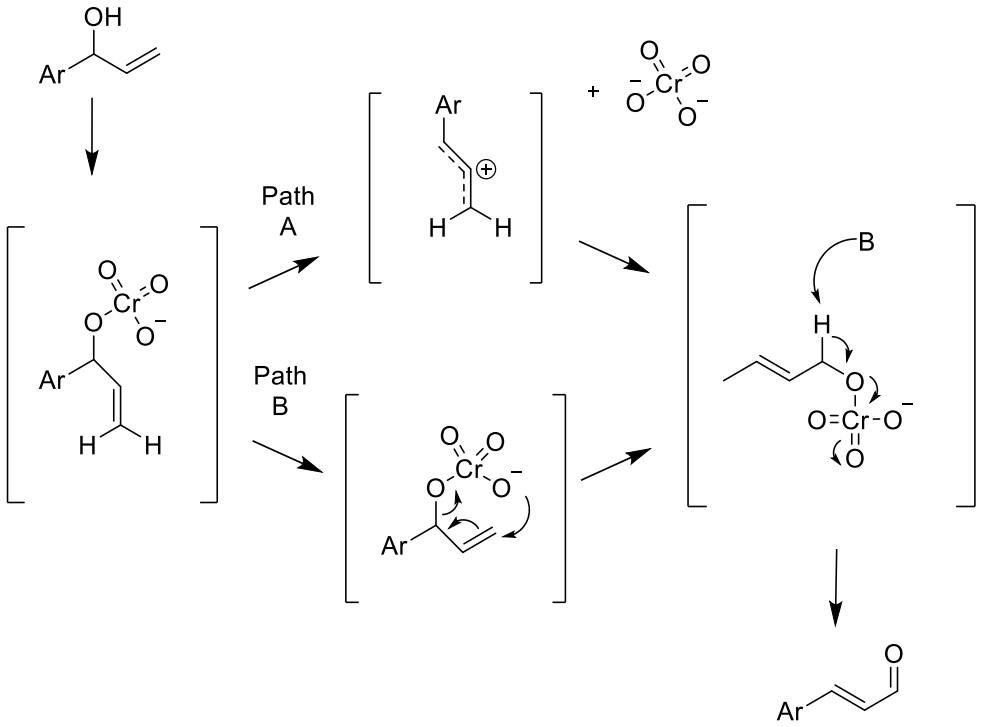


Figure 2.33 Two proposed mechanism by Killoman and group for the carbonyl transposition of the unconjugated benzylic alcohol into the conjugated E-cinnamaldehyde derivative.

3,3'-Rearrangements such as the Claisen rearrangement can be catalyzed by the use of Lewis acid (Lambert & MacMillan, 2002). When periodic acid was used alongside PCC during the oxidation, Killoran and co-workers in 2016, were able to obtain the carbonyl transposition derivative without the expected ketone.

CHAPTER III

METHODOLGY

General Procedures and Instrumentation

All chemical compounds were purchased from Sigma-Aldrich Chemical Company and used without further purification unless otherwise noted. Anhydrous tetrahydrofuran was prepared by drying over 4 Å molecular sieves under an inert atmosphere of argon for at least 72 h prior to use.

Reactions were monitored with thin layer chromatography which was performed on glass-backed silica gel coated plates containing a fluorescent indicator (Silica gel 60 A, Partisil EH6F). Compounds were visualized using a handheld UV lamp.

Methods for purification of reaction products included flash chromatography and radial chromatography. Flash chromatography was performed on a Yamazan *Smart Flash* EPCLC al-5805 with TLC image reader Re-X10. The compounds were loaded onto a small inject column containing silica gel adsorbent and a medium (23 X 123 mm) universal column containing silica gel (16 g, 40 µm particle size). The compounds were isolated using gradient ratios of ethyl acetate:hexanes solvents as the eluent.

Column Chromatography was performed on a column with a diameter of 1.5”. To the column 0.5” of sand was added followed by 6” of silica gel and

topped with 0.25” sand. A fixed ratio of 80:20 hexane:ethyl acetate was used as the mobile phase.

Radial chromatography was performed on prepared 1 mm or 2 mm silica gel plates using a Harrison Associates Chromatotron (model number 7924T) with a fixed ratio of hexane:ethyl acetate solvents as the mobile phase.

The compounds where identified by comparison to known compounds using spectroscopic analysis. Spectroscopic analysis of all compounds was performed in $CDCl_3$ on a Bruker Avance II FT-NMR (400 MHz for ^1H). Infrared spectra were obtained using a single crystal ATR (zinc selenide) FT-IR Nicolet Is5.

Preparation of Substituted Alcohols

Commercially available substituted benzaldehydes (**1a-e**) were used as the starting material and treated with vinylmagnesium bromide in anhydrous THF in order to obtain substituted 1-phenyl-2-buten-1-ols (**2a-e**) (see Figure 3.1). The Grignard reaction was monitored by TLC using 80:20 hexane:ethyl acetate as the eluent. If required, the product was purified after extractive isolation using chromatography by either flash chromatography or radial chromatography. The pure product was identified and confirmed by comparison to literature data using ^1H -NMR spectroscopy.

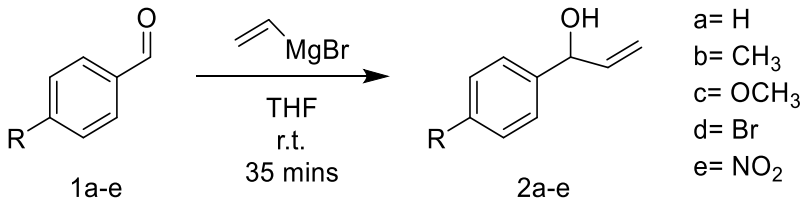


Figure 3.1 Grignard synthesis of secondary carbinol

Preparation of Substituted Ketones

Oxidation of the series of substituted 1-phenyl-2-propen-1-ols (**2a-e**) to the corresponding ketones was accomplished using pyridinium chlorochromate (PCC) in a slurry of dichloromethane containing magnesium sulfate as a support phase (Figure 3.2). Trituration and filtration provided the crude product mixture. Radial and preparatory flash chromatography were employed as methods for purification.

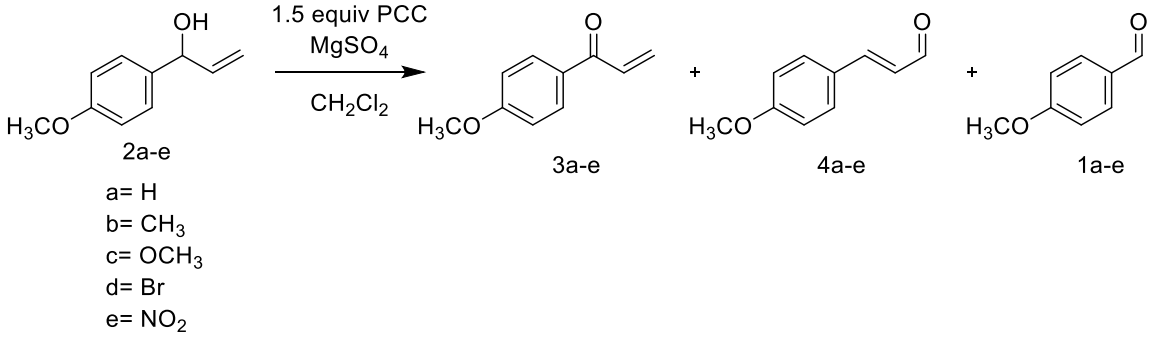


Figure 3.2 Oxidation of secondary alcohol with PCC

Alternative Oxidation Methods

Alternative methods of oxidation were initially explored in order to evaluate the product distribution and effect of oxidant. After each reaction, the quantity and identity of the expected ketone and other by-products were determined by ^{1}H-NMR spectroscopy. Confirmation of the product identity was accomplished by comparison of the spectroscopic data with known compounds.

Oxidation Over Time

The oxidation of **2c** was monitored by ^{1}H -NMR over the course of two hours to note the formation of the products of the reaction over time. The general procedure involved addition of 1.0 equivalent **2c** to a rapidly stirred solution of 16 equivalents $MgSO_4$ and 1.5 equivalents PCC in dichloromethane. Aliquots of the reaction mixture were removed every 5 minutes for the first 20 minutes and then at 60 minutes. This was done by stopping the stirring, waiting 15 seconds, and then removing the aliquot by Pasteur pipet. The stirring was restarted immediately upon removal of the aliquot. The aliquot was added to a screwcap vial prefilled with diethyl ether and stored on ice. The aliquot was then filtered through a pad of Florisil (60-100 mesh) and rinsed with additional diethyl ether.

Each of the individual aliquots were transferred with additional diethyl ether to a roundbottomed flask and evaporated using the rotary evaporator (held at 40 °C) for 10 minutes under vacuum. The samples were placed in the freezer for 24 hours until evaluation using ^{1}H-NMR spectroscopy.

At the end of two hours, the remainder of the reaction was quenched by diluting with diethyl ether. This was then filtered in a manner similar to the individual aliquots. This sample was also stored in the freezer until its evaluation using ^{1}H-NMR spectroscopy.

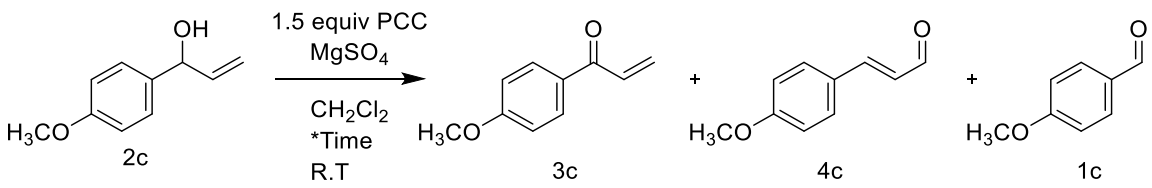
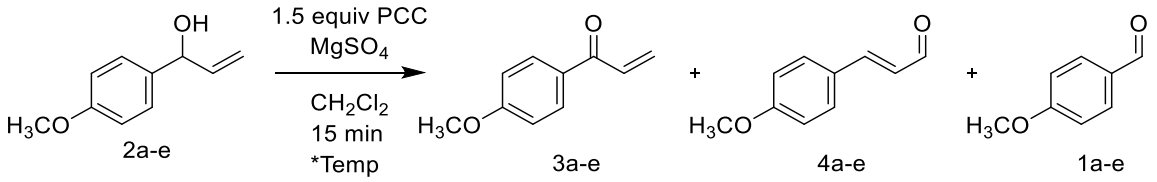


Figure 3.4 Chromium oxidation of 1-(*p*-methoxyphenyl)-2-propen-1-ol (**2c**).
*Aliqouts were removed every five minutes for 20 minutes and at 1 hour.

Oxidations at Varying Temperatures

The PCC oxidation of **2** was monitored and evaluated as a function of the reaction temperature. Three temperatures were studied in detail. The reaction was studied under reflux, ambient room temperature, and in an ice bath.

The general procedure for the oxidation at all temperatures is as follows. The reaction was brought to the appropriate temperature before the addition of 1.0 equivalent of the substituted alcohol (**2a-d)**, to the temperature-adjusted and stirred slurry of 1.5 equivalents PCC and 16 equivalents $MgSO_4$ in dichloromethane. After 15 min, the reaction was quenched by the addition of diethyl ether. The solution was allowed to stir for 5 minutes before filtering through a pad of Florisil (mesh 60-100). The flask was rinsed three times with additional diethyl ether and the rinses passed through the Florisil pad. The filtrate was transferred to a tared screwcap vial with diethyl ether. The solvents were removed by rotary evaporation and the vial was stored in the freezer prior to ^{1}H-NMR analysis. For the reaction under reflux the solution was removed from heat and allowed to cool prior to quenching the reaction at 15 minutes with ether.



a= H
b= CH_3
c= OCH_3
d= Br
**e= NO_2

Figure 3.4 Chromium oxidation of unsaturated benzylic alcohols with 1.5 equiv PCC. *Temperatures used in this study included: 38 °C, 20 °C, or at 5 °C. **Reaction was maintained at room temperature for 15 minutes and then held at 38 °C for an additional 30 minutes.

CHAPTER IV

RESULTS

A series of 1-phenyl-2-propen-1-ols (**2a-e**) were prepared to determine the ratio of expected product and by-products when they underwent reaction with a chromium oxidizer such as PCC. This was accomplished by first treating a series of substituted aldehydes with a solution of vinylmagnesium bromide in tetrahydrofuran (THF) to form **2a-e**. The alcohols were then oxidized with pyridinium chlorochromate (PCC) to afford the expected vinyl ketone (**3a-e**), transposed cinnamaldehyde derivative (**4a-e**), and oxidatively cleaved benzaldehyde derivative (**1a-e**). The overall reaction sequence is shown in Figure 4.1.

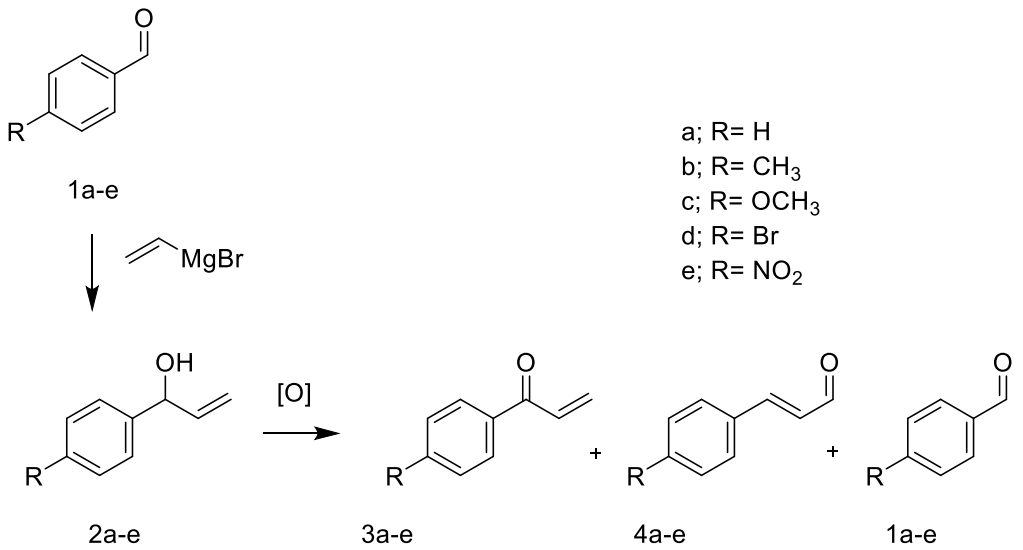
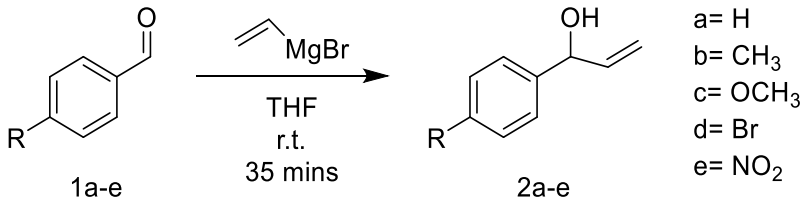


Figure 4.1 Overall reaction schematic.

Grignard Addition of Vinyl Alcohol

The preparation of a series of 1-phenyl-2-propen-1-ols (**2a-e**) was performed on both 1 g and 5 g scales. For example, a 1 g-scale preparation of **2a** was accomplished by adding 14 mL (14.4 mmol, 1.5 equiv) vinylmagnesium bromide (1.0 M in THF) via syringe to 0.957 mL (9.42 mmol) benzaldehyde (**1a**) in 25mL anhydrous THF. The addition occurred over a 15-minute period and the temperature of the solution was maintained slightly above room temperature. An ice-bath was available to cool the reaction if the temperature got too high.

After the addition was complete, the reaction was stirred at room temperature for 30 min. The reaction was then quenched by the addition of 25 mL water and stirring was continued for 15 min. The product of the reaction, 1-phenyl-2-propen-1-ol (**2a**) was isolated by extraction using ethyl acetate. Thin-layer chromatography (silica gel, 80:20 hexanes:ethyl acetate) indicated that the product of the reaction required chromatographic separation to obtain spectroscopically pure product. The product (**2a**) was transferred to a vial for storage with diethyl ether.



1a-e 2a-e

Figure 4.2 Grignard addition of a vinyl group

The reaction was repeated for a series of benzaldehydes that differed in the electronic character of the R group located para to the aldehyde functionality. The electronic character was varied from strongly electron withdrawing (NO_2) to

strongly electron donating (OCH_3). This was done to explore the effect of electronic character on the chromium oxidation reactions. In this way, the crude average yield of the alcohols **(2a-e**) ranged from 88 to 99+% as shown in Table 4.1. Each reaction was attempted multiple times and the average yield recorded. The yields given for **2c** and **2e** were not provided as an average and instead represent only the highest yield of the product obtained. Substituent electronic effects did not appear to influence the yield of the reaction. Any variability in the product yield was instead attributed to traces of water in the glassware or syringes used in the reaction, because they were not flame dried under an inert atmosphere. In addition, water could exist in the starting material as the benzaldehydes were used without purification. Any water present in the reaction during the addition of the vinylmagnesium bromide would quench the Grignard reagent.

Table 4.1

*Grignard reaction yields for **2a-e.***

Compound	R	% yield
2a	-H	99+
2b	$-CH_3$	99+
2c	$-OCH_3$	99+[a]
2d	-Br	88
2e	$-NO_2$	99+[a]

[a] Indicates that the average percent yield over multiple trials could not be calculated.

The crude percent yields, determined prior to chromatographic separation, in many cases were above 100%. This was likely due to the presence of solvent

in the sample. Evidence of this was noted by the presence of ethyl acetate and diethyl ether used in the extractive isolation of the compound in the ^{1}H-NMR spectrum for the specific compound. For example, Figure 4.3 shows significant solvent peaks at 4.2 ppm, 3.5 ppm, labeled X corresponding to ethyl acetate and diethyl ether respectively. The remaining signals in the ^{1}H-NMR were evaluated to confirm the structure of the vinyl carbinols. For example, Figure 4.3 illustrates the signals for compound **2d**. A para-substituted benzene ring provides the signals at 7.5 ppm and 7.3 ppm. The alkene functional group can be seen as a multiplet at 6.0 ppm, and then at 5.4 ppm and 5.2 ppm. The carbinol hydrogen merges with the alkene signal at 5.2 ppm. The unlabeled broad singlet at 4.7 ppm was assigned as the OH group in the molecule.

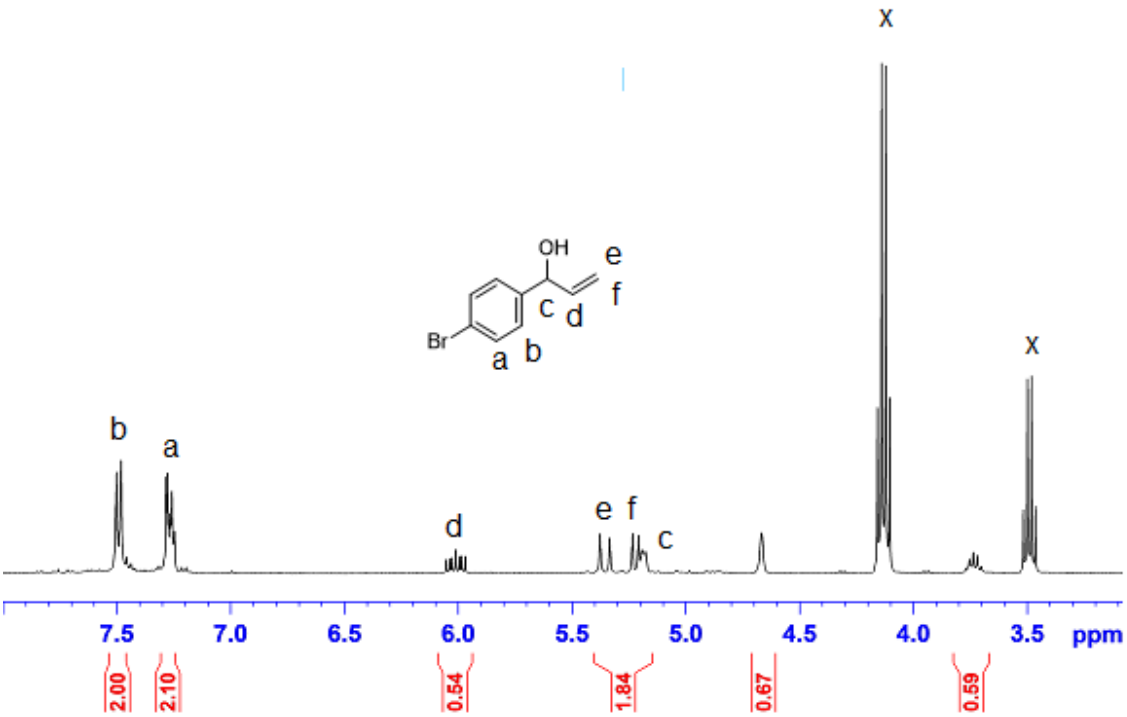


Figure 4.3 Proton NMR of 2d demonstrating presence of solvent labelled X.

Each of the products, **2a-e**, were also evaluated for purity by examination of their IR spectrum. A small amount of each sample was placed directly onto a zinc-selenide ATR crystal in the FTIR. Based on a comparison of the starting material and product, it was predicted that the IR should show a loss of a carbonyl signal and the addition of a C-O stretch for a secondary alcohol. In addition, a H-O absorption at 3300 cm^{-1} and an sp^3 C-H absorption around 2950 cm^{-1} would be expected to appear. However, the presence of ethyl acetate in **2d** can be seen in the IR at 1250 cm^{-1} and 1700 cm^{-1}. This causes the signals due to the product to be very difficult to distinguish from the solvent and starting material

signals, as seen in Figure 4.4. The sp^3 C-H stretch around 2950 cm^{-1} was also identified in the IR spectrum likely also as a result of the ethyl acetate. An OH stretch indicative of an alcohol or residual water could be seen in the IR spectrum around 3500 cm^{-1}. Due to the complicated spectrum, the IR was not used as a confirmation of formation of the end product.

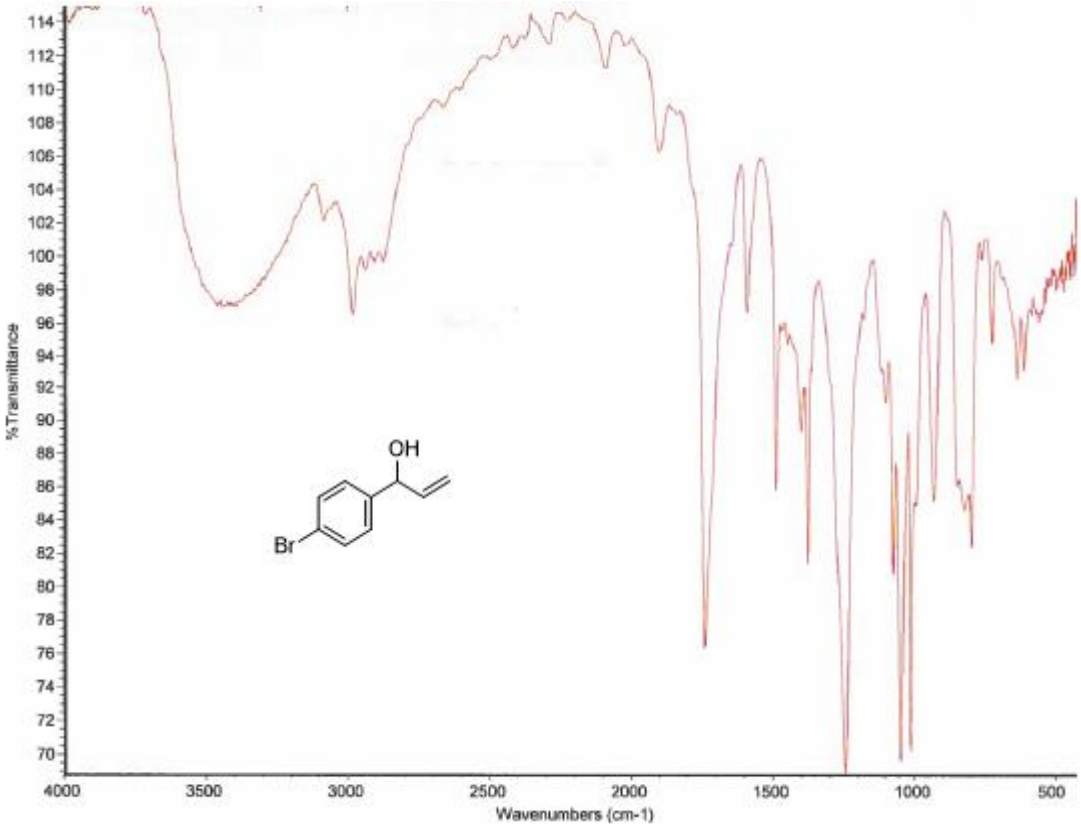


Figure 4.4 IR of **2d** demonstrating the presence of solvent.

The addition of a vinyl group was confirmed via analysis of the 1H -NMR spectrum. For example, analysis of compound **2c** reveals the alkene as a complex multiplet at 6.06 ppm and two doublets at 5.45 ppm and 5.18 ppm (Figure 4.5). The signal at 5.18 ppm overlaps the carbinol hydrogen. The para-substituted benzene is observable at 7.30 ppm and 6.90 ppm. The methoxy group appears as a singlet at 3.82 ppm. The presence of ethyl acetate can be

seen as a quartet at 4.24 ppm. The absence of signals from the starting aldehyde indicated the reaction had gone to completion. Detailed spectral data for the series of compounds can be found in Appendix A.

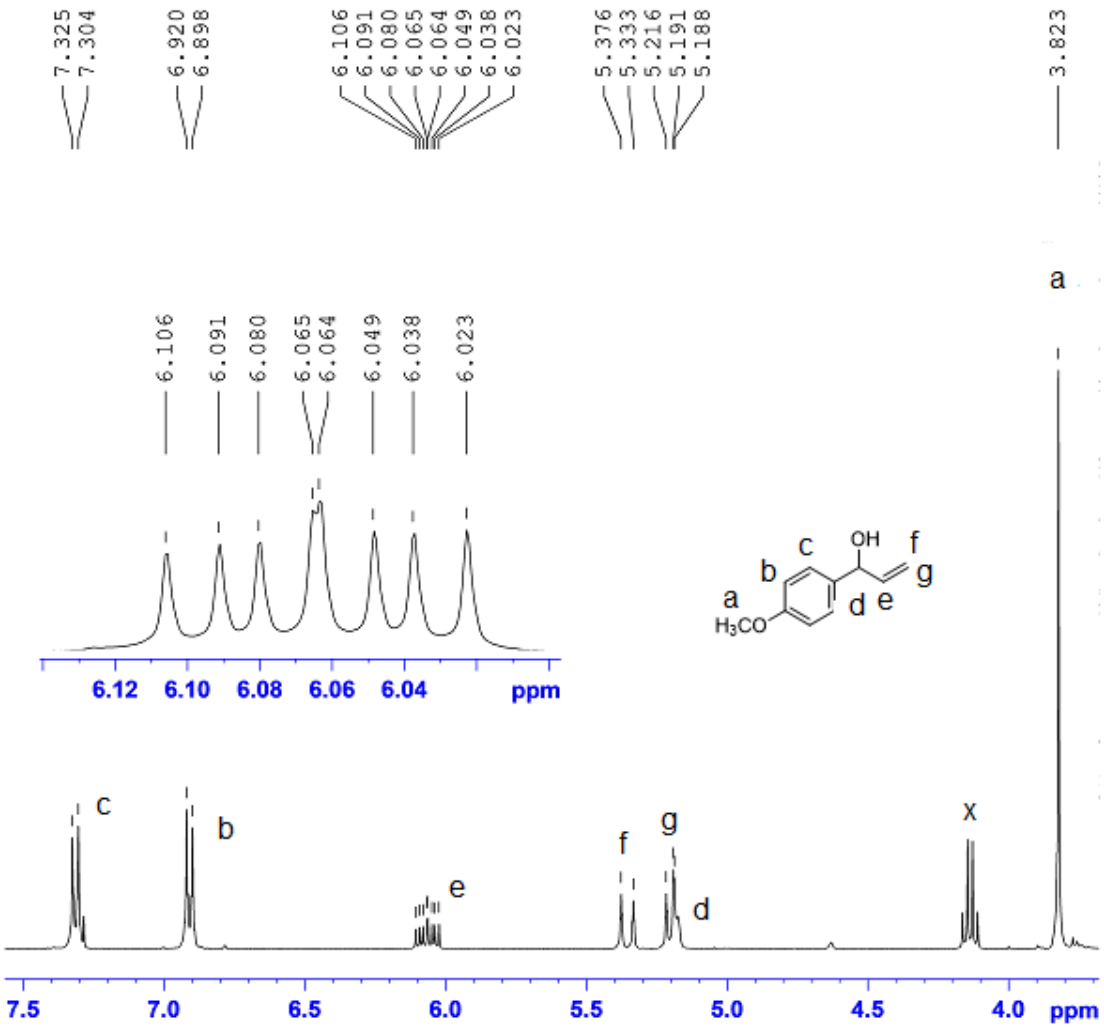


Figure 4.5 Proton NMR spectrum of 2c illustrating the Grignard addition had gone to completion

The products were isolated from the crude reaction mixture using flash chromatography on the Yamazen Smart Flash system or with radial chromatography. Analysis of the product mixture by TLC revealed the best solvent system to use for the separation. Most of the products were isolated with a gradient elution from 100 % hexanes to a mixture of 8:2 hexanes:ethyl acetate.

The compounds were loaded onto a small inject column (silica gel) and the separation was performed using a medium universal column of silica gel.

As seen above in Table 4.1, **2c** and **2d** gave the best yields resulting in a 1H -NMR that was relatively free of impurities with the exception of extraction solvent that was not removed during rotary evaporation. The deactivating substituents **2d** and **2e** resulted in the lowest yield of the corresponding 1-phenyl-2-propen-1-ol. This could likely be due to the fact that the corresponding starting benzaldehydes for these two substituents were solids rather than liquids and may have contained traces of water. The product **2e** proved to be the most difficult to isolate. Extraction and rotary evaporation resulted in the formation of a dark product that partially crystalized as a brown oil. 1H -NMR analysis of one of the Grignard additions **2e,** as seen below in Figure 4.6, showed that the Grignard additions resulted in only a small conversion to the expected unsaturated product this was seen in all cases that **2e** was used.

Key signals for the *p*-nitrobenzaldehyde **1e** can be seen in the crude 1H -NMR spectrum (Figure 4.6). Specifically, the aldehyde hydrogen appears as a singlet at 10.18 ppm and the two doublets that indicate α,β-substituted benzene ring can be seen at 8.10 ppm and 8.42 ppm. Another *p*-substituted aromatic product dominates the product mixture. Those key signals occurred at 7.56 ppm and 8.35 ppm, this aromatic by-product (labeled X) was not isolated. The identity of this by-product was believed to be *p*-nitrobenzyl alcohol when the spectra was compared to that of literature value (SigmaAldrich, CAS 619-73-8). The expected unsaturated ketone **3e** was observed as well in the 1H -NMR spectrum as a

multiplet at 6.0 ppm, and the terminal alkene functional group was observable as a doublet at 5.4 ppm and another doublet at 5.3 ppm. The carbinol hydrogen overlaps the doublet at 5.3 ppm.

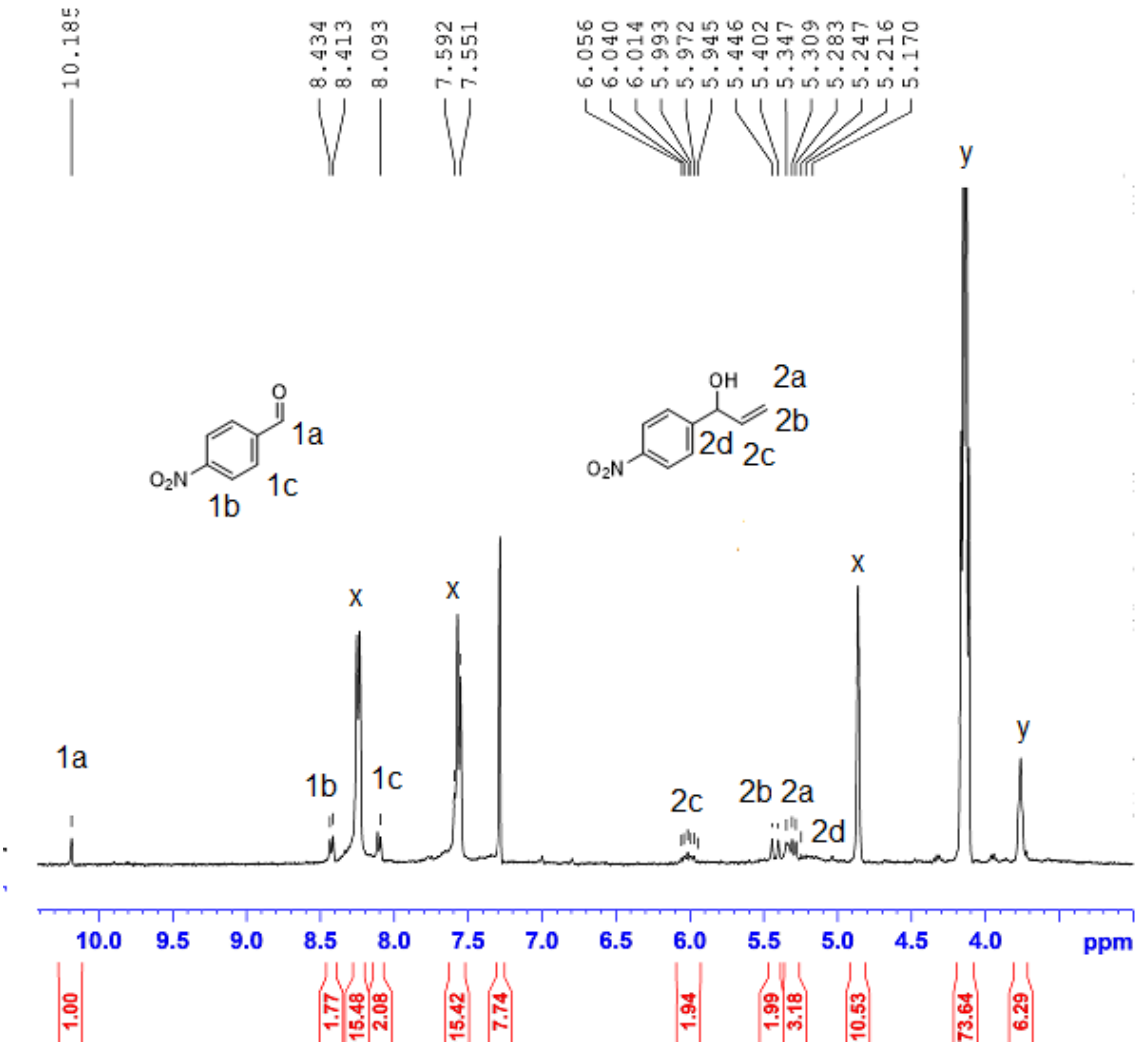


Figure 4.6 NMR of 2e after Grignard addition

The desired product **2e** was isolated from the reaction mixture after flash chromatography. The ^{1}H-NMR spectrum is shown in Figure 4.7. Doublets at 8.24 ppm and 7.58 ppm indicated a para-substituted benzene. An unresolved doublet of doublets of triplets (ddt) can be seen at 6.01 ppm that corresponds to the internal hydrogen on the alkene. A first-order doublet can be seen at 5.43 ppm

corresponding to one of the terminal alkene hydrogens. Two overlapping signals at 5.32 ppm correspond to a terminal alkene hydrogen and to the carbinol hydrogen.

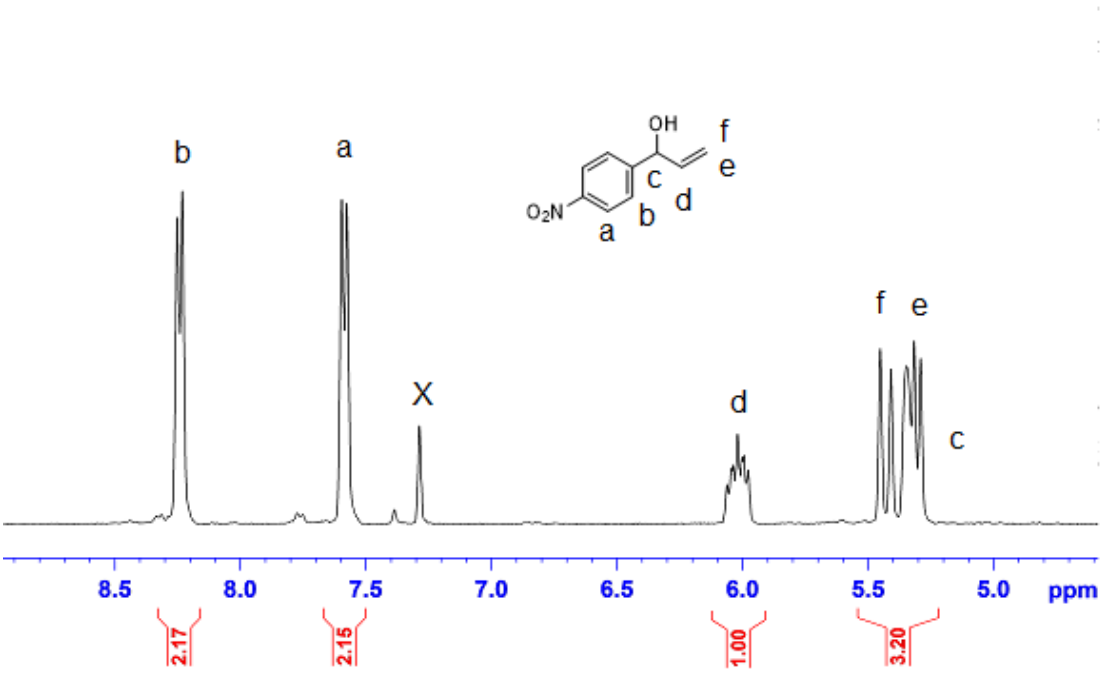


Figure 4.7 ^{1}H-NMR spectrum of compound **2e** recovered after purification via flash chromatography.

Alternative Oxidation Methods

Oxidation of the allyl alcohol was attempted using many different oxidants (Figure 4.8). The expected products included the desired ketone (**3**), the transposed aldehyde (**4**) and the oxidatively cleaved product (**1**). These oxidations were explored for preliminary purposes and yields were not calculated for any of the products. Specifically, the use of sodium hypochlorite, nickel peroxide, manganese dioxide, and hydrogen peroxide were each briefly

examined as oxidizing agents for the benzylic allyl alcohols. The spectral data can be found in Appendix 2 and will be discussed briefly.

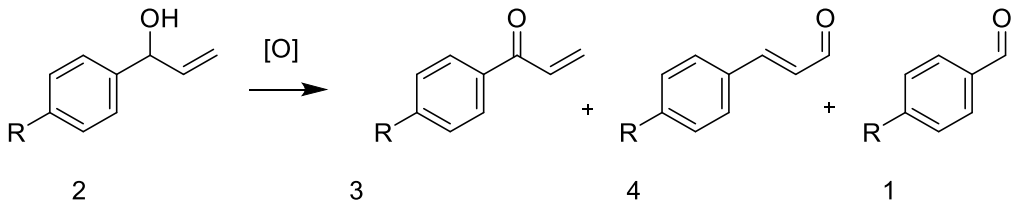


Figure 4.8 Alternative oxidation methods were examined to test for the oxidation transposition and oxidative cleavage potential of different oxidants.

Sodium hypochlorite (NaOCl) oxidation of **2b** (Figure 4.9) was completed in an Erlenmeyer flask at room temperature with stir bar. The alcohol, **2b,** (1.7 mmol) was suspended in 11 mL acetone to give a final concentration of 0.15M. Then, 1 mL glacial acetic acid was added followed by 6 mL of bleach (~6% NaOCl solution). The reaction was monitored by TLC using 8:2 hexane:ethyl acetate as the eluent. After 30 minutes, the reaction was quenched by the addition of 10 mL hexane.

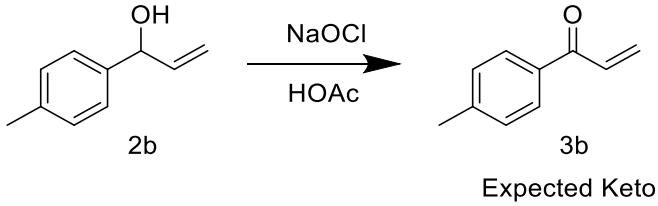


Figure 4.9: Sodium hypochlorite oxidation of p-methylphenyl vinyl carbinol

The organic layer was extracted with hexane twice. The combined organic phases were washed with 10 mL aqueous saturated sodium carbonate and twice with water. The organic layer was dried over anhydrous magnesium sulfate, filtered by gravity, and the solvent removed by rotary evaporation. The ^{1}H-NMR spectrum that was obtained indicated the presence of the benzaldehyde

derivative (**1b**) that likely arose via oxidative cleavage of the starting material, as well as other unidentified products. The expected ketone was not observed as seen in Figure 4.10.

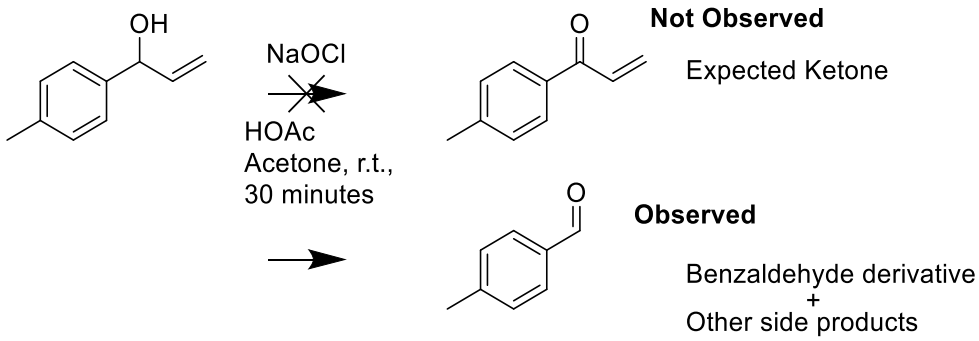


Figure 4.10 Oxidation of **2b** in NaOCl did not result in formation of the expected α,β-unsaturated ketone.

The use of nickel peroxide as an oxidizing agent for the benzyl vinyl carbinols was explored. Nickel peroxide was prepared immediately before use by dissolving 0.01 mol of NaOH in 3.5 mL of a 6% NaOCl solution. Once fully dissolved, nickel(II) sulfate (1.3 g) dissolved in 35 mL water was added dropwise with stirring. Over the course of 15 minutes, the solution turned dark black and a solid precipitated. The precipitated nickel peroxide was isolated by suction filtration through a sintered-glass funnel and washed with water. No further purification was attempted. The use of the recovered nickel peroxide as an oxidizer was explored using compound **2c** as shown below in Figure 4.11.

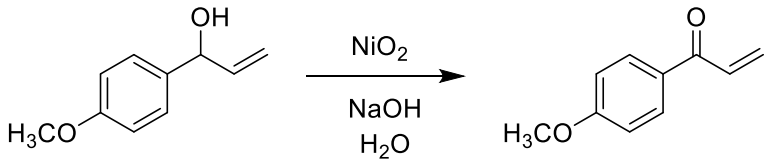


Figure 4.11 Oxidation of p-methoxyphenyl vinyl carbinol

To a round bottom flask was added 45 mL of 0.14 M NaOH. Then, 3.14 mmol **2c** was added with stirring followed by 1.45 g nickel peroxide. The resulting solution was stirred at room temperature for 50 min. Over the course of the reaction, the solution turned from black to green. The solution was then gravity filtered and the filtrate extracted twice with 10 mL diethyl ether. The combined organic phases were washed with water, dried over anhydrous $MgSO_4$, and the solvent removed by rotary evaporation. A 1H -NMR spectrum was obtained for the crude reaction mixture. The benzaldehyde derivative (**1c**) was observed as a singlet at 9.9 ppm. The oxidation of **2c** with nickel peroxide did not produce the expected α,β-unsaturated ketone as seen in Figure 4.12. A large amount of starting material was still present in the reaction mixture as well as other unidentified side products (see Figure A2.2 in Appendix 2).

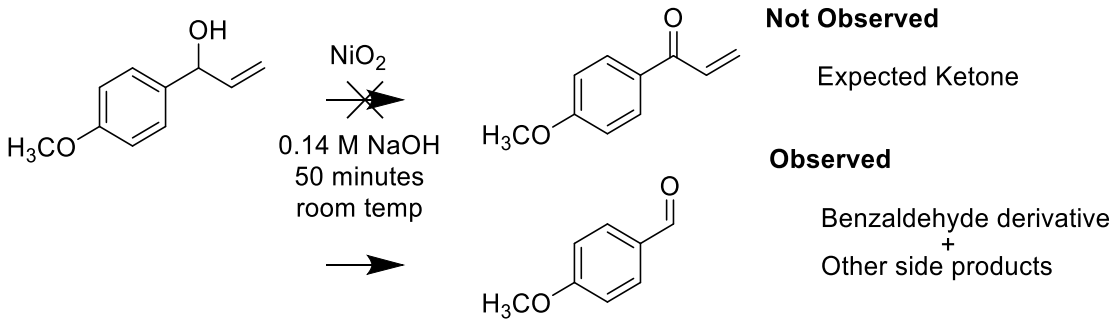


Figure 4.12 Oxidation with nickel peroxide

Oxidation of **2c** was also explored with MnO_2. To an oven-dried 100 mL roundbottom flask was added 1.3 g MnO_2, 50 mL of chloroform, and a stirbar.

The solution was stirred vigorously. To this solution was added 0.256 g of compound **2c**. The reaction mixture was monitored by TLC using 8:2 hexane:ethyl acetate as the eluent. No noticeable products were made by examination of the TLC after 1 hr. After 24 hours, the reaction was vacuum filtered through a plug of sand in a sintered glass funnel and the solvent was removed by rotary evaporation. None of the expected products were observed in the ^{1}H-NMR spectrum; only the starting material was recognizable in the spectrum. These results are summarized in Figure 4.13.

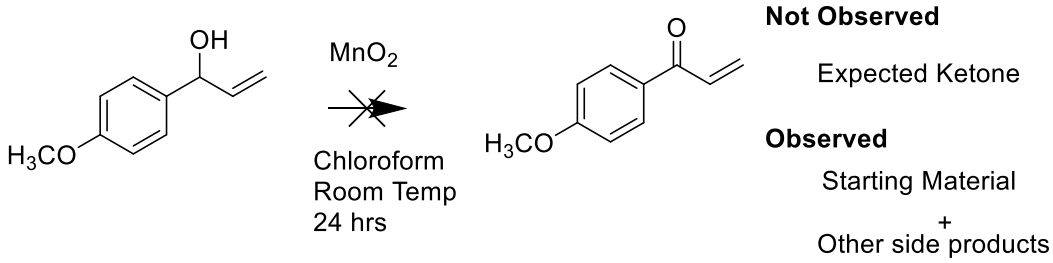


Figure 4.13 Oxidation using manganese dioxide

The use of MnO_2 with a co-oxidant was examined as shown in Figure 4.14. This was attempted by adding 0.53 g 1-(*p*-methylphenyl)-2-propen-1-ol (**2b**) to a roundbottom flask containing 5 mL of water. Then, 10 mL of 30% H_2O_2 was added and the solution refluxed for 20 minutes. The solution was cooled and 0.067g MnO_2 was added. The solution was refluxed again for 40 minutes, then stirred at room temperature for 24 hours. The reaction mixture was extracted with 30 mL ethyl acetate. The organic phase was washed once with water, once with brine, dried over anhydrous magnesium sulfate, and filtered by gravity. The solvent was removed by rotary evaporation and a ^{1}H-NMR spectrum was obtained. Unfortunately, the starting material and the expected products were not

observed. Instead, the spectrum indicated the loss of the alkene functional group (see Figure A2-4 in the Appendix).

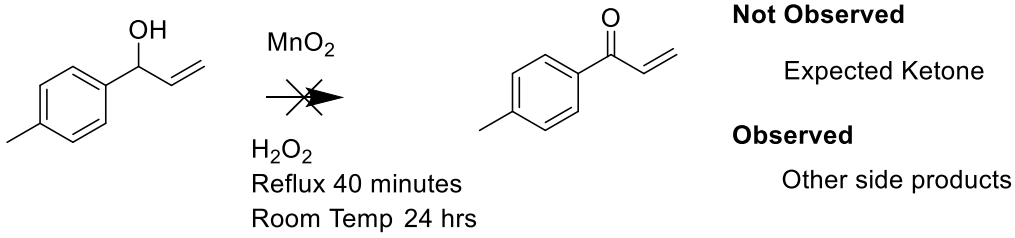


Figure 4.14 Oxidation with MnO_2

Oxidations using Pyridinum Chlorochromate

Chromium(VI) was investigated as an oxidizing agent on the phenyl vinyl carbinols at varying temperatures. The reaction was also explored as a function of time.

For example, compound **2c** was explored in the oxidation reaction with chromium(VI) using pyridinium chlorochromate (PCC) as the oxidant. To a 25 mL round bottom flask was added 1.07 g (4.98 mmol) PCC and 3.20 g (26.6 mmol) anhydrous $MgSO_4$. Then, 11 mL dichloromethane was added and the mixture stirred vigorously to suspend the slurry. To this mixture, 0.542 g (3.30 mmol) **2c** was added and the solution was monitored by thin layer chromatography using a 8:2 hexane:ethyl acetate eluent. After 15 minutes of vigorous stirring, the solution was quenched by the addition of 10 mL diethyl ether, and allowed to stir for an additional 7 minutes. The solution was then filtered through a sintered-glass funnel containing a pad of Florisil (2.41 g). The flask was washed three times with a total of 15 mL diethyl ether that was also passed through the pad of Florisil. The combined filtrates were concentrated under vacuum on the rotary

evaporator for 20 minutes. The sample was stored in the freezer prior to ^{1}H-NMR analysis.

The reaction outcomes for the PCC oxidation were analyzed via ^{1}H-NMR spectra of the crude reaction mixtures. Figure 4.15 indicates the hydrogen atoms used for the assignment of the individual components in the reaction mixtures. Each hydrogen atom was chosen based on its ability to be completely separated from other signals in the 1H -NMR spectra. The relaxation delay used during acquisition of the spectra was adjusted from 3 to 10 seconds and the integration values of the resulting signals evaluated at both delays. No significant difference in the integration values was observed when the relaxation delay was adjusted, indicating that the relaxation mechanisms (T1 and T2) were similar for all hydrogen atoms considered for the evaluation of the reaction outcome. This allowed the ^{1}H-NMR spectra to be obtained with the shortest relaxation delay (3 seconds) without fear of integration values being affected

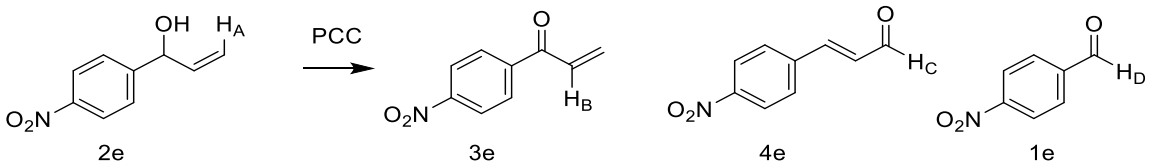


Figure 4.15 PCC oxidation of the benzyl vinyl carbinol **2e**. The hydrogen atoms used for ^{1}H-NMR analysis are labeled.

The hydrogen signals used for the analysis were selected as baseline separated signals that integrated for a single hydrogen atom in each of the compounds in the reaction (Figure 4.14). As an example of the separation of the signals and their baseline resolution, Figure 4.15 illustrates the chemical shift for each of the hydrogen atoms. The mole ratios of the compounds corresponding to

H_a, H_b, H_c, and H_d, were determined based on the integration values of the specified hydrogens in the mixture of products.

An example of the application of this evaluation is shown in Figure 4.16. This spectrum was generated after oxidation of the nitro derivative. Specifically, the starting material (**2e**) was treated with PCC by the method previously described and monitored by TLC with a mobile phase of 8:2 hexanes:ethyl acetate. After 15 minutes no conversion was observed and the solution was brought to reflux for an addition 30 minutes. The reaction was quenched with ether and filtered through a pad of Florisil. The expected ketone (**3e**) was the predominant product labeled H_b. A small amount of the benzaldehyde derivative (**1e**) was observed as labelled H_d. A small amount of transposition product (**4e**) was also observed as H_c.

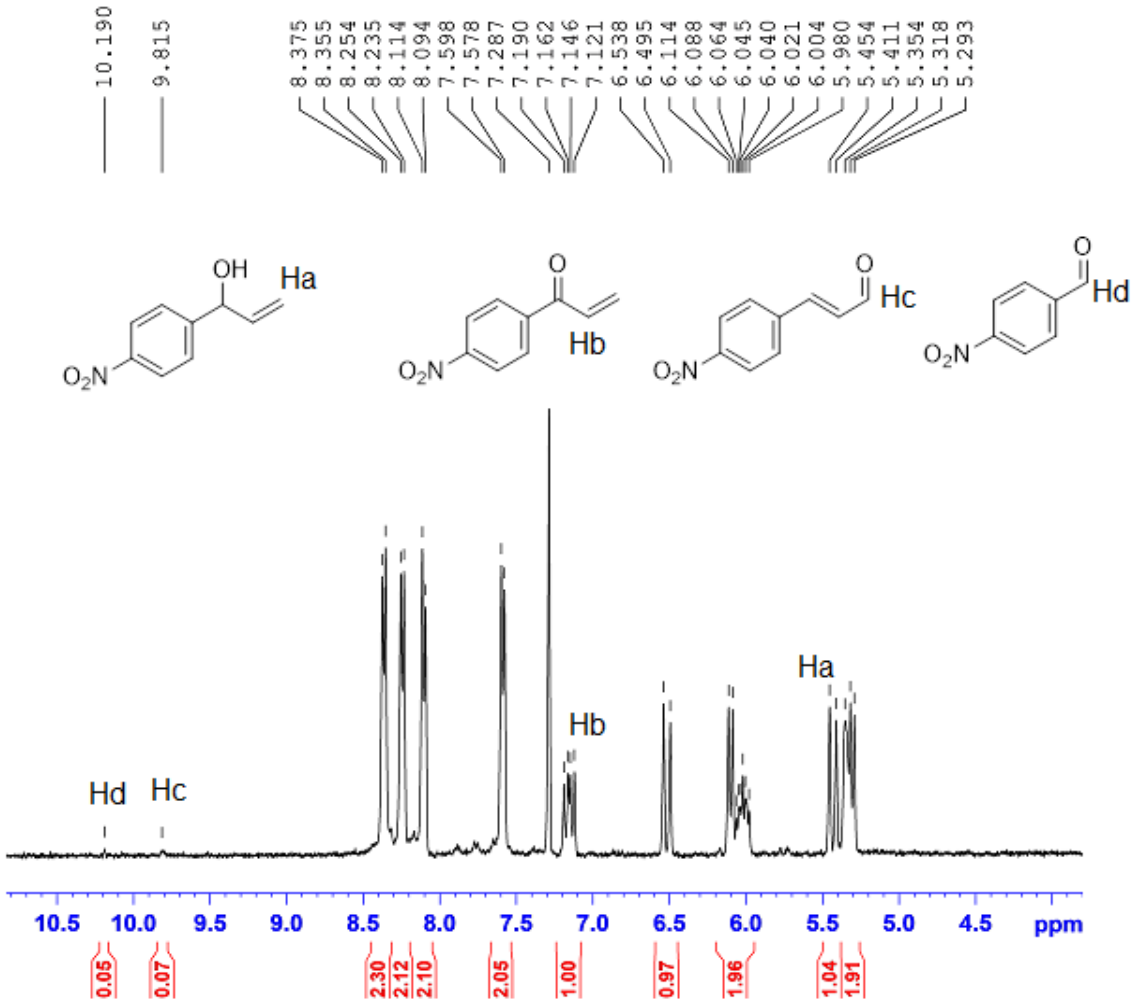


Figure 4.16 Oxidation of 2e under reflux. Hydrogen signals used to calculate the yield of each component in the reaction are labeled.

The percent of each of the compounds found in the products were calculated as a percentage of starting materials present in the ^{1}H-NMR. Equation 4.1 and 4.2 demonstrate how the percent conversion was determined. Equation 4.3 demonstrates how the overall NMR yield was calculated. In addition, the integration values were used to compare the different products obtained in each reaction. The conversion of **2e** after 45 minutes was found to be 52 %. With an

overall NMR yield for ketone **3e** of 89 %. The equations below demonstrates how this information was obtained.

Equation 4.1

$$\% \text{ Recovered Starting Material} = \frac{H_a}{(H_a + H_b + H_c + H_d)}$$

Where…

H_a = the integration value of the signal at 5.42 ppm;

H_b = the integration value of the signal at 7.15 ppm;

H_c = the integration value of the signal at 9.82 ppm; and,

H_d = the integration value of the signal at 10.19 ppm.

Equation 4.2

$$100 - \% \text{ Recovered Starting Material} = \% \text{ Conversion}$$

Equation 4.3

$$\text{NMR Yield} = \frac{H_b}{(H_b + H_c + H_d)} \times 100\ \%$$

Time Monitored Chromium Oxidation

The *p*-methoxy derivative (**2c**) was chosen for the time-monitored oxidation using PCC. This compound was chosen when a preliminary study indicated that the signals in the ^{1}H-NMR spectrum were relatively free of impurities. In addition, the spectrum indicated the ample formation of all products during the oxidation.

Monitoring the formation of products during the reaction involved setting up the experiment in a very reproducible way. The following procedure was used for each of the trials. To a 25 mL-round bottom flask was added 15.2 mL dichloromethane and 0.205 g (1.25 mmol) **2c**. This mixture was stirred during the slow addition of 2.402 g (19.9 mmol) anhydrous magnesium sulfate. Then, powdered PCC (0.406 g, 1.88 mmol) was added in one portion and the stirring continued until the PCC was well dispersed in the slurry (less than 5 seconds). Immediately thereafter, the stirring was stopped and a 1-mL aliquot of the reaction was removed and added to a screwcap vial prefilled with 2 mL diethyl ether. Addition of the reaction to the diethyl ether immediately quenched the reaction by precipitating unreacted PCC from the reaction mixture. The vial was stored in an ice-bath until it was worked up.

In the same fashion, 1-mL aliquots of the reaction were removed during the course of the reaction. Specifically, at 30 seconds prior to the removal of the aliquot, the stirring was stopped to allow the magnesium sulfate to settle and a 1-mL aliquot was added to a separate screwcap vial containing 2 mL diethyl ether. Samples were removed every 5 minutes for the first 20 minutes. Then, a sample was removed at 1 hr.

Each aliquot was worked up by filtering the contents of each screwcap vial through a sintered glass funnel containing a pad of Florisil (1.3 g, 60-100 mesh). After filtration, the filter was rinsed with an additional 5 mL of diethyl ether. The combined filtrate was then concentrated under vacuum and stored in the freezer until it could be analyzed by ^{1}H-NMR spectroscopy.

The remaining reaction mixture was diluted to twice its volume with diethyl ether at the end of 2 hours of reaction time. The brown slurry was vacuum filtered through a pad of Florisil (60-100 mesh) with additional ether. The filtrate was then evaporated to dryness using a rotary evaporator and stored in the freezer until the sample could be analyzed ^{1}H-NMR spectroscopy.

Analysis of the ^{1}H-NMR spectrum allowed for the rapid identification of the products formed in the reaction. This was accomplished by comparison of the integral values of the hydrogen atom signals that correspond to the individual components of the product mixture (as shown previously in Figure 4.14). The three products and the overall conversion rate for a series of trials of the reaction are illustrated in Figure 4.17. The data used to prepare the graph shown in Figure 4.17 is included in Appendix 1.

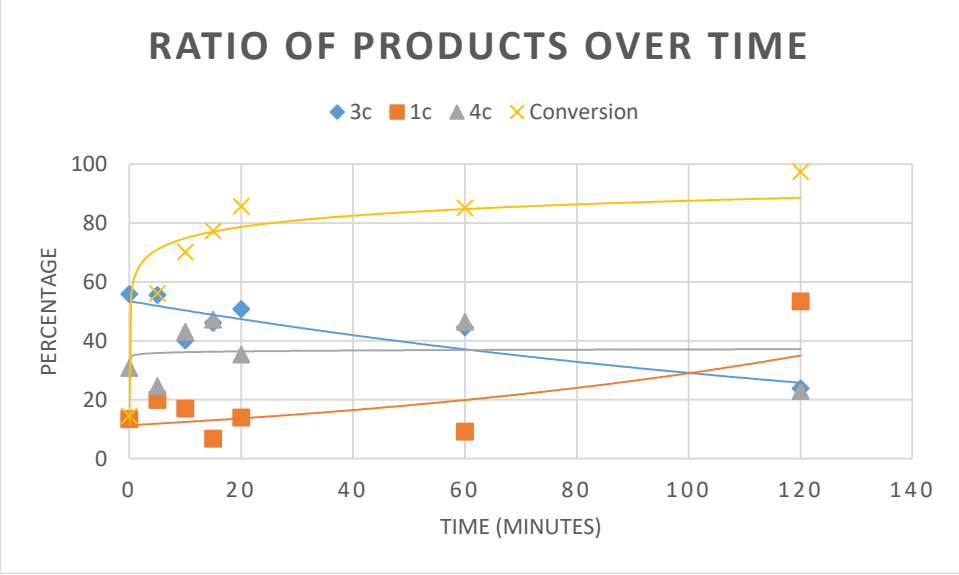


Figure 4.17 Ratio of products versus time during the PCC oxidation of **2c** to give the expected ketone **3c**, the transposition product **4c**, and the benzaldehyde derivative **1c**

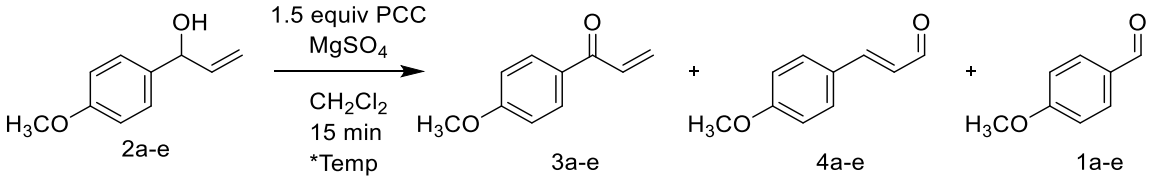
It was observed during the oxidation of **2c** that the reaction began as soon as the PCC was added to the swirling alcohol-$MgSO_4$ mixture. This was visually observed as an immediate color change from orange to a darkening orange. The solution continued to turn dark brown over the course of the reaction.

Based on the data in Figure 4.17, the starting material was nearly completely consumed within the first 15 to 20 minutes. The ratio of the products, however, continued to change after this time of the reaction. The percent of expected ketone product is greatest immediately after the start of the reaction, and declines steadily over the course of the 2-hour exposure to the reaction conditions. At the end of the first hour, the ratio of transposition product and the expected ketone were comparable. In fact, the percent of transposition product appears to be relatively constant during the reaction. This is likely due to the fact that the transposition product has a fully conjugated pi system while the expected ketone is cross-conjugated. The oxidative cleavage product, the benzaldehyde derivative (**1c**), increases over time even once the reaction has reached completion. Given that the transposition product (**4c**) appears to remain constant throughout the course of exposure to the PCC, the likely source of the oxidative cleavage product is the expected ketone (**3c**).

Temperature Monitored Chromium Oxidations

The oxidation of para-substituted phenyl vinyl carbinols was examined at varying temperatures. The reactions were completed in an ice bath (5 °C), at room temperature (20 °C), and under reflux with dichloromethane (~38 °C). The variations between the product ratios allowed for comparisons to be made versus

the temperature and product substitution. Insights on the effects of the electronic withdrawing and donating properties of the reactants can also be made. The reaction time for each oxidation was held constant at 15 minutes with the exception of **2e**. Figure 4.18, demonstrates all the substituents evaluated over varying temperature.



*a= H
b= CH_3
c= OCH_3
d= Br
**e= NO_2

Figure 4.18 Oxidation of benzylic alcohols at varying temperature. *Represents that the compound was prepared with 50 mg. **Represents that the compound was not repeated at three different temperatures.

A purified sample (8 mg) of **2e**, was oxidized using the standard procedure (Figure 4.19). After 15 minutes at room temperature, TLC analysis of the reaction mixture indicated that the oxidation of **2e** had not provided any measureable product. The round bottom flask was then transferred to a hot water bath and maintained at 40 °C for an additional 30 minutes. The volume of the reaction mixture in the round bottom was doubled with diethyl ether and then filtered through a sintered-glass funnel containing a pad of Florisil (60-100 mesh) and rinsed with additional diethyl ether. Of the product recovered, only about 40% of the starting material was oxidized after the 45 minutes.

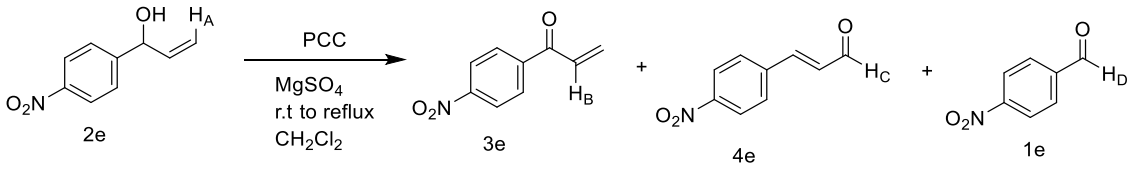


Figure 4.19 PCC oxidation of the phenyl vinyl carbinol 2e. The hydrogen atoms used for H-NMR analysis are labeled.

The transposition product **4e** and the initial p-nitrobenzaldehyde **1e** where the minor products as evidenced by the crude ^{1}H-NMR (Figure 4.20). A 52 % conversion of compound **2e** into the three products was observed. The α,β-unsaturated ketone was the primary ketone with an 89 % yield at the end of the 45 minutes. Due to the relatively low purity of the oil and the low reactivity of the para-nitro compound, the reaction was not duplicated in an ice bath, or at room temperature.

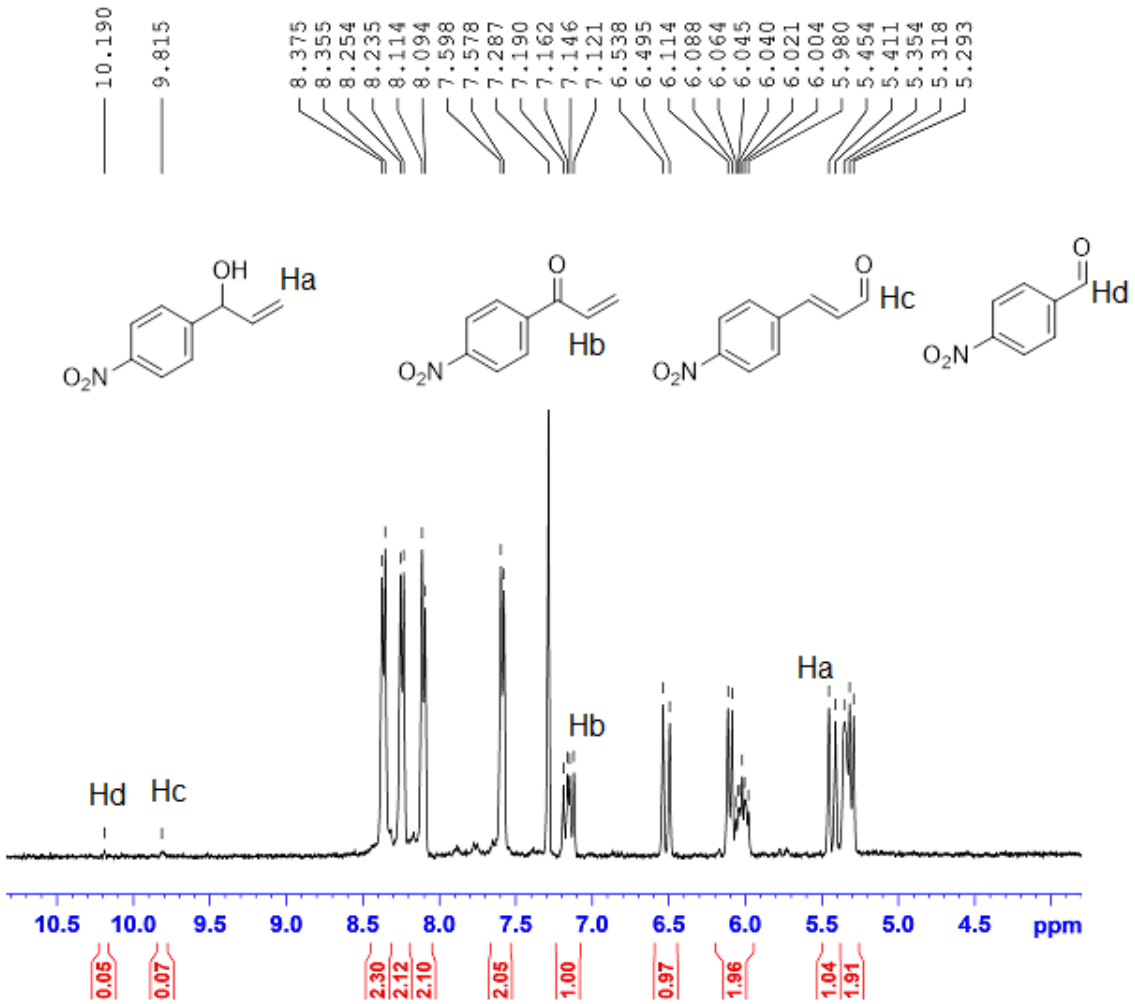


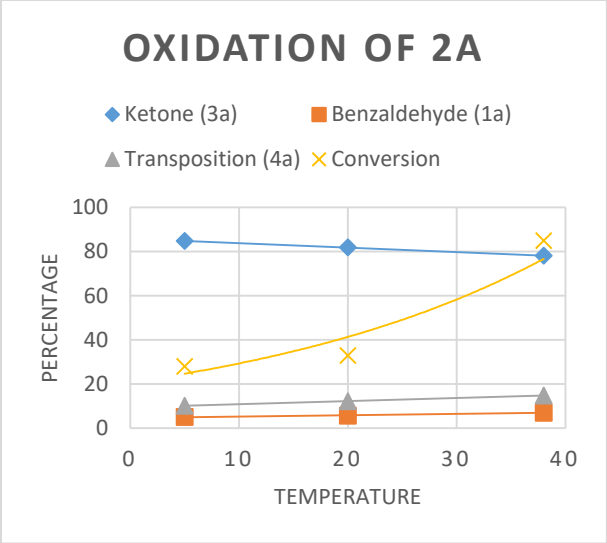
Figure 4.20 Oxidation of P-NO_2 compound

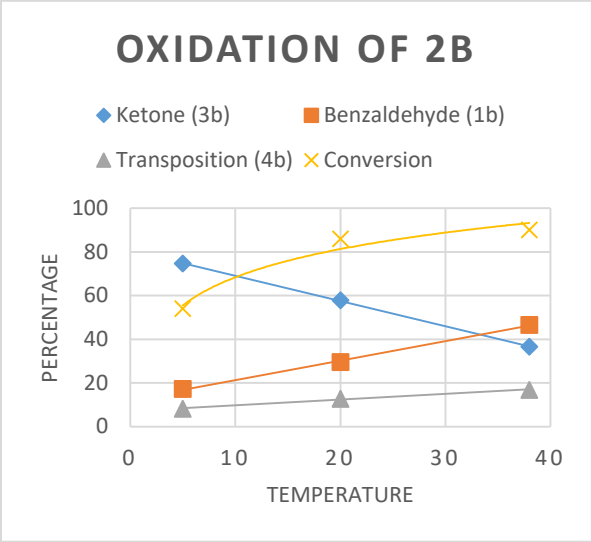
Compound **2a** was purified using flash chromatography prior to oxidation. The reaction was carried out in a 15 mL round bottom with a total of 7 mL dichloromethane. Isolated **2a** (69 mg) was added to a stirred solution of anhydrous magnesium sulfate (0.509g, 4.2 mmol) and PCC (0.168g, 0.78 mmol) in 7 mL dichloromethane. The solution was maintained in a water-ice bath at 5°C over the course of the reaction. After 15 minutes, the solution was quenched by the addition of 5 mL diethyl ether and stirred for 5 minutes. The solution was then

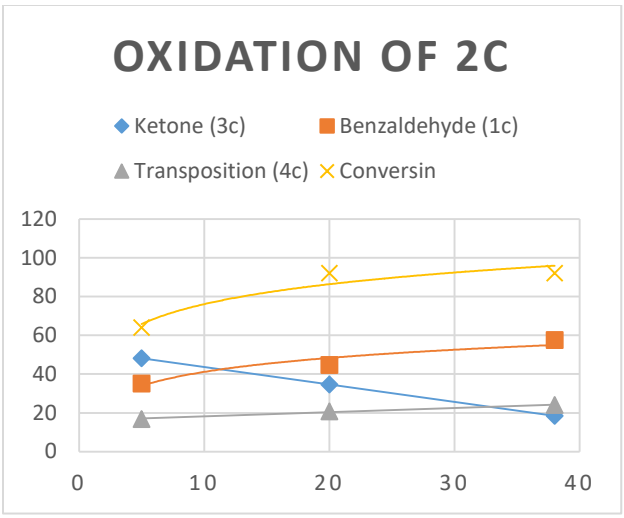
suction filtered through a pad of Florisil (1.519 g) and rinsed with an additional 10 mL diethyl ether. The filtrate was transferred to a tared vial and evaporated to dryness using a rotary evaporator. The vial was stored in the freezer until it could be analyzed via ^{1}H-NMR spectroscopy.

Compounds **2b**, **2c**, and **2d** were not purified prior to PCC oxidation. Each was oxidized in a 1.0:1.5 ratio of **2a-e**:PCC. The reaction was carried out in a total of 13 mL dichlormethane in a 25 mL round bottom submerged in an ice bath at 5°C. As an example, **2c** (0.542 g) was added to a chilled stirred solution of anhydrous magnesium sulfate (3.206 g, 26.6 mmol) and PCC (1.074 g, 4.98 mmol). After 15 minutes, the reaction was quenched by the addition of 10 mL diethyl ether and allowed to stir for 5 min. The reaction was then filtered through a pad of Florisil (2.408g) and rinsed with 15 mL diethyl ether. The filtrate was evaporated to dryness under vacuum and stored in the freezer until it could be analyzed by ^{1}H-NMR spectroscopy.

Compounds **2a,b,c,d** were oxidized at three temperatures. The reaction was maintained in either an Ice bath (5 °C), room temperature (20 °C), or under reflux with dichloromethane (38 °C). The trials of each reaction performed under reflux conditions were removed from the heat and allowed to cool prior to quenching the reaction. Each oxidation was quenched with the appropriate amount of ether after 15 minutes. The average results of the trials are shown above in Figure 4.21.


OXIDATION OF 2A
Ketone (3a)
Benzaldehyde (1a)
Transposition (4a)
Conversion
PERCENTAGE
100
80
60
40
20
0
0
10
20
30
40
TEMPERATURE


OXIDATION OF 2B
Ketone (3b)
Benzaldehyde (1b)
Transposition (4b)
Conversion
PERCENTAGE
100
80
60
40
20
0
0
10
20
30
40
TEMPERATURE



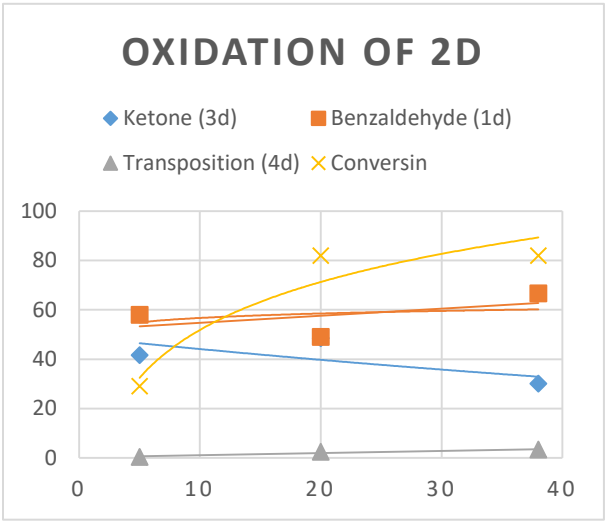


Figure 4.21 Plots of the oxidation products at varying temperatures. **2a*** was separated using flash chromatography prior to oxidation. Oxidation of **2a-d**, to obtain the expected ketone **3a-d**, the transposition product, **4a-d**, and the benzaldehyde derivative, **1a-d**.

The ^{1}H-NMR determined conversion to the expected ketone in all of the oxidations decreased as the temperature of the reaction increased. The oxidations completed in an ice bath showed the highest percentage of starting material. The conversion of starting material increased as the temperature increased. This higher conversion, however, led to a decrease in the expected

ketone and an increase in the side products. An optimal temperature for conversion of the starting material and NMR yield can be derived from the data in Table 4.2. The optimal temperature for the reaction appears to be at a lower temperature to obtain the expected ketone (**3a-d**). Elevated temperatures give a higher yield of transposition product (**4a-d**) and benzaldehyde derivative (**1a-d**). The oxidation of **2a** shows that optimal conversion was reached at higher temperature. **2a** was completed in a 50 mg scale as opposed to 500 mg scale as seen with the oxidation of **2b-d**.

Table 4.2

*Ratio of products observed in each oxidation normalized to the expected ketone **3a-d**.*

2	Temperature (°C)	3: 4 : 1	Conversion (%)	NMR Yield (%)
a[a]	5	1: 0.12: 0.06	28	85
a[a]	20	1: 0.15: 0.07	33	82
a[a]	38	1: 0.19: 0.09	85	78
b	5	1: 0.11: 0.23	54	75
b	20	1: 0.22: 0.51	86	57
b	38	1: 0.46: 1.27	90	37
c	5	1: 0.35: 0.73	64	48
c	20	1: 0.60: 1.29	92	35
c	38	1: 1.31: 3.13	92	18
d	5	1: 0.01: 1.39	29	42
d	20	1: 0.05: 1.01	82	49
d	38	1: 0.11: 2.22	82	30
e[b]	20-38	1: 0.07: 0.05	52	89

[a] indicated reaction was completed on a 50 mg scale. [b] indicates that the reaction exceeded the 15 minutes.

The electronic substituent effects were examined from these data. The trends observed in the oxidations show that the activation of the system with electron donating substituents encouraged the formation of the transposition product. Figure 4.22 demonstrates how the activating properties of the para

substituent may have led to a higher yield of transposition product. Stabilization of the carbinol carbon, encouraged the shift of pi electrons to conjugate the system.

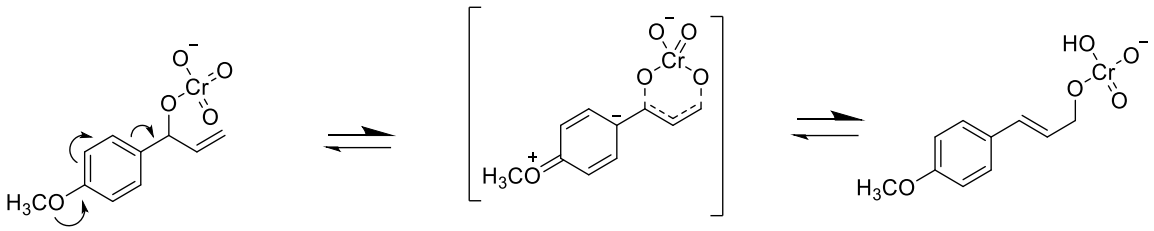


Figure 4.22 Demonstration of carbonyl transposition with an electronic donating substituent.

Compound **2e** gave the lowest yield of transposition product. It is likely that the electronic withdrawing characteristics of the para-nitro group caused the overall lowest yield of transposition product. Figure 4.23 demonstrates the electronic withdrawing effects of the para nitro group on the ring.

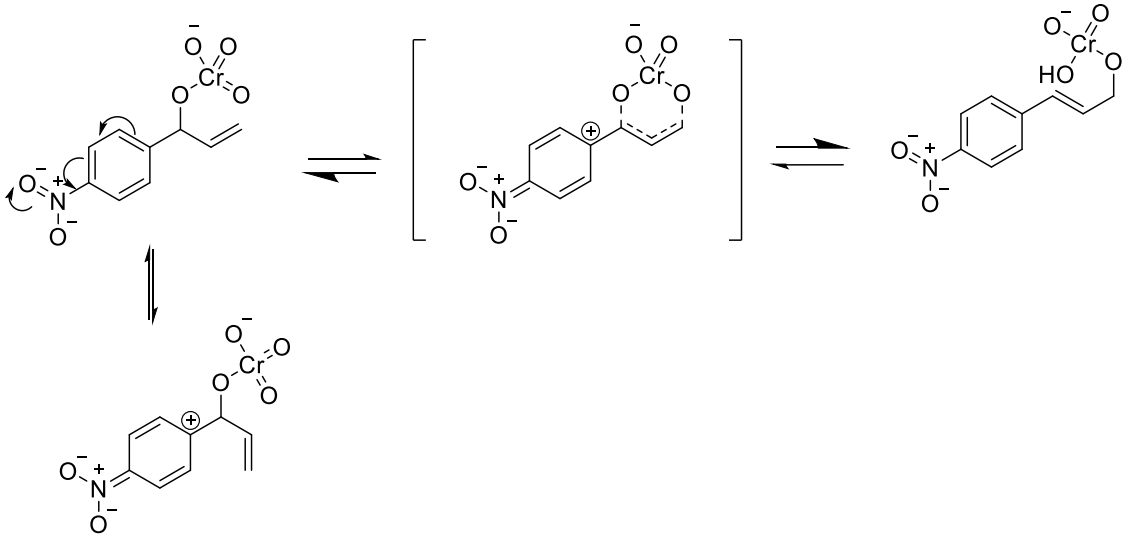


Figure 4.23 Demonstration of carbonyl transposition with an electronic withdrawing substituent.

The Hammett values for the different substituents were plotted against the yield of transposition product to demonstrate the electronic effects on the formation of the transposition product. The Hammett Values for the different substituents are given in Table 4.3 below (Hansch, Leo, & Hoeckman, 1995).

Table 4.3

Hammett sigma-p value (σ_p) for substituents used in this study

R	Hammett Value
$-OCH_3$	-0.27
$-CH_3$	-0.17
-H	0
-Br	0.23
$-NO_2$	0.78

A plot of Hammett sigma-p (σ_p) versus the yield of transposition product illustrates a negative slope to the correlation. This implies that the electron donating ability of substituents increases the yield of the transposition product (**4a-e**). The slope of a linear correlation of the data (see Figure 4.23) is -0.44. This value is equivalent to the Hammett rho value (ρ). A ρ value of -0.44 indicates electron donating groups have a slight positive impact on the outcome of the reaction.

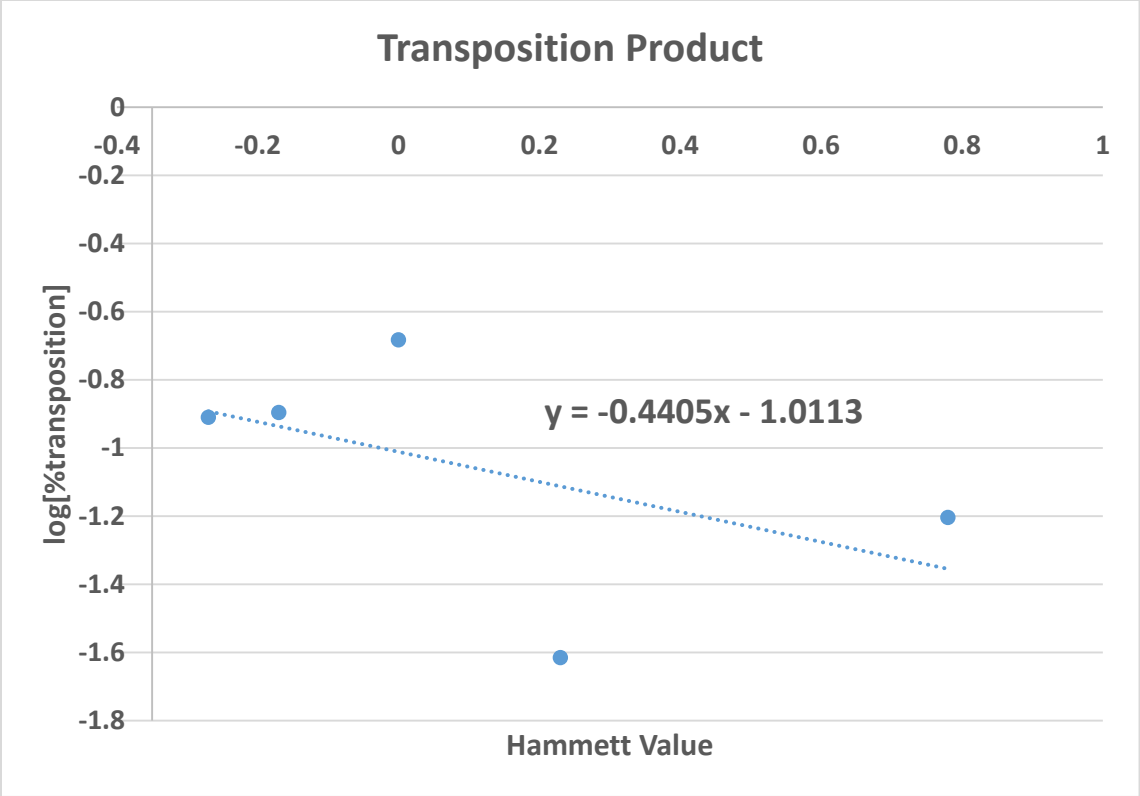


Figure 4.24 Hammett plot of the yield of the reaction versus the electronic character for the formation of the transposition product (**4a-e**)

Compounds **2b**, **2c** and **2d** were all completed in comparable concentrations of PCC. Compounds **2b** and **2c** were both activating and ortho, para directing, while **2d** was deactivating. Of the three starting alcohols at comparable concentrations **2d** gave had the lowest conversion of starting material although not significantly lower than the oxidation of **2b** and **2c** at every temperature. The oxidation of **2d** also led to the highest yield of benzaldehyde derivative (**1d**) at every temperature. As the temperature of the reaction mixture increased the ratio of the transposition product increased as well for all compounds as seen previously in Table 4.2. The result for the ratio of the transposition product of **2d** under reflux was comparable to that of the more

deactivating **2e**. These results are indicative of how electron withdrawing groups will have a significant effect on transposition as seen previously in Figure 4.24.

Our results are comparable with the results by Killoran that electron donating groups gave the lowest yield of the benzaldehyde derivative (**1a-e**) side product as well as the highest yield of transposition product (**4a-e**) (Kiloran et al., 2010). Kiloran's proposed mechanism further agrees with our findings and proposed mechanism. Specifically, it is possible that the higher yield of transposition product may be due to the weakening of the carbon alcohol bond favoring the elimination of the bond and the increased nucleophilicity encouraged the shift of pi electrons in the chromate carbonyl to the alkene during the 3,3-sigmatropic rearrangement. When electron withdrawing groups are used, the carbon-oxygen bond is strengthened by the slightly positive characteristic of the ring, resulting in a lower yield of transposition product.

CHAPTER V

CONCLUSION

Chromium(VI) has previously been shown to cause oxidative transposition during oxidation of vinyl benzylic alcohols. The PCC reagent (a source of chromate, Cr(VI)) was explored as an oxidizing agent to explore the utility of a terminal $\alpha,\beta-$unsaturated system to undergo carbonyl transposition. A series of $\alpha,\beta-$unsaturated phenyl carbinols were prepared via a Grignard addition of the vinyl group to the corresponding benzaldehydes. The product mixture that resulted from the PCC oxidation was analyzed by ^{1}H-NMR. Evaluation of the reaction was accomplished as a function of time, temperature, and substituent electronic character.

Preliminary studies of other common oxidizing agents were unsuccessful in the production of the expected ketones, **3a-e**. In addition, preservation of the vinyl group was not maintained in any of the alternative reactions. The common oxidizing agents studied were not suitable candidates for the preparation of the expected ketone (**3a-e**) or the transposition product (**4a-e**).

Shorter reaction times with PCC appear to give a greater quantity of expected ketone (as evidenced in the reaction of **2c** to **3c**). Longer reaction times also appear to have an effect on the ratio of products. Longer reaction times

show an increase in the benzaldehyde derivative (as evidenced in the reaction of **2c** to **1c**).

To analyze the compounds as a function of temperature, each PCC oxidation was maintained for 15 minutes. The conversion of starting material was observed to increase at higher temperatures and appeared to decrease with an increase in temperature. The optimal conditions for the reaction to obtain the expected ketone (**3a-d**) appears to be that of lower temperatures, although the conversion of starting material to the expected ketone is sacrificed with a lower overall conversion. Elevated temperatures result in a higher percent conversion of the starting material, but also resulted in a higher yield of transposition product (**4a-d**) and benzaldehyde derivative (**1a-d**).

Based on the data obtained from the exploration of the PCC oxidation, electronic character has a significant effect on the formation of the transposition product (Table 4.22). Starting materials containing substituents that were electron donating resulted in a higher yield of the transposition product at every temperature. The groups that were electronic withdrawing, however, resulted in a lower conversion of starting material.

These results have led to the proposed mechanism (shown in Figure 2.33) where the electronic character of the substituent results in the placement of a partial charge on the atom next to the carbinol carbon. If that partial charge is negative, the reaction proceeds toward the loss of the oxygen at the carbinol, followed by oxidation at the end of the conjugated system. If that partial charge is

positive, the oxidation occurs at the carbinol to form the cross-conjugated system.

Future work for this research could include attempts to buffer the system with acid/base to monitor for the formation of products. By adjusting the reaction conditions, the mechanism for the chromium transposition may be further explored. Additionally, examining the formation of the benzaldehyde derivative using an O-18 labeled alcohol would determine whether the oxygen is retained in the products or lost. Retention or loss of the O-18 during oxidative cleavage to form the benzaldehyde derivative could give insight into mechanism involved in the reaction (Figure 5.1).

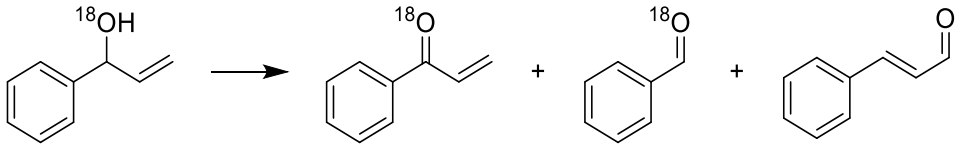


Figure 5.1 Oxidation of α,β–unsaturated benzylic alcohols with labeled oxygen

Further confirmation of the proposed mechanism could be explored by isolating each of the three products and subjecting each to the conditions of the PCC oxidation. This would confirm the oxidative cleavage occurring after the product has been oxidized and would confirm which compound is responsible for the transformation.

Finally, adding substituents to the terminal alkene may give insight into the oxidative transposition of secondary unsaturated alcohols where cross-conjugation would exist in both products. For example, PCC oxidation of

substituted 1,3-diphenyl-2-propen-1-ols would result in a cross-conjugated product for the expected ketone and the transposition product.

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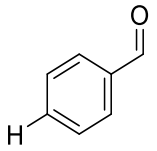
APPENDIX A

COMPOUND DATA

Compound Data

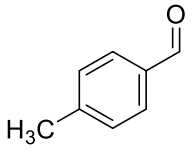
Starting Materials:
All of the initial benzaldehydes were purchased from Sigma Aldrich.

Benzaldehyde Derivative



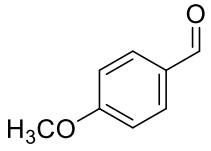
1a

Benzaldehyde
Analysis of a reaction mixture showed how the spectroscopic data agreed with that found in the literature (SigmaAldrich CAS 100-52-7). ^{1}H NMR (400 MHz, $CDCl_3$) δ in ppm 10.05 (s, 1H), 7.91 (d), 7.60 (t), 7.50(d)



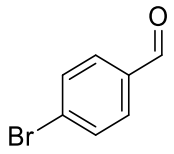
1b

4-Methylbenzaldehyde
Analysis of a reaction mixture showed how the spectroscopic data agreed with that found in the literature (SigmaAldrich CAS 104-87-0). ^{1}H NMR (400 MHz, $CDCl_3$) δ in ppm 9.98 (s, 1H), 7.79 (d, 2H, J= 7.6 Hz), 7.35 (d, 2H, J=7.2 Hz), 2.46 (s, 3H)



1c

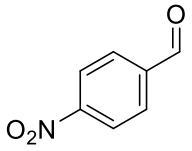
4- Methoxybenzaldehyde
Analysis of a reaction mixture showed how the spectroscopic data agreed with that found in the literature (SigmaAldrich CAS 123-11-5). ^{1}H NMR (400 MHz, $CDCl_3$) δ in ppm 9.92 (s, 1H), 7.87 (d, 2H, J= 7.6 Hz), 7.04 (d, 2H, J=8 Hz), 3.89 (s, 3H)



1d

4-Bromobenzaldehyde

Analysis of a reaction mixture showed how the spectroscopic data agreed with that found in the literature (SigmaAldrich CAS 1122-91-4). ^{1}H NMR (400 MHz, $CDCl_3$) δ in ppm 10.00 (s, 1H), 7.77(d, 2H, J= 7.6 Hz), 7.71 (d, 2H, J=8 Hz)



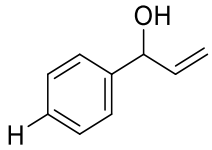
1e

4-Nitrobenzaldehyde

Analysis of a reaction mixture showed how the spectroscopic data agreed with that found in the literature. (SigmaAldrich CAS 555-16-8). ^{1}H NMR (400 MHz, $CDCl_3$) δ in ppm 10.19 (s, 1H), 8.43 (d, 2H, J= 7.6 Hz), 8.11 (d, 2H, J=8 Hz)

General Procedure for the Grignard Reaction

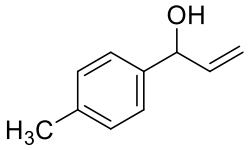
To an oven dried 100-mL roundbottom containing a stirbar was added (8.3 mmol, 1 equiv) p-toluylaldehyde into anhydrous THF (25 mL) at room temperature and maintained under argon. Vinyl magnesium bromide (9.2 mmol, 1.1 equiv) was added via syringe into the roundbottom with an argon purged needle over the course of 5 minutes. After 35 minutes the reaction was quenched with H_2O (25 mL). The organic layer was extracted 3 times with (20 mL) ethyl acetate. The organic layer combined and washed twice with (20 mL) H_2O and then dried over anhydrous $MgSO_4$. The solution was then gravity filtered and concentrated under vacuum to give a crude oil.



2a

1-Phenyl-2-propen-1-ol

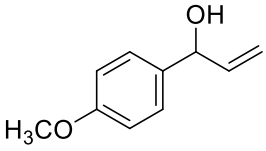
Analysis of a reaction mixture showed how the spectroscopic data agreed with that found in the literature (SigmaAldrich CAS 4393-06-0). Purification of the oil was completed using column chromatography 80:20 hexane:ethyl acetate. ^{1}H NMR (400 MHz, $CDCl_3$ δ in ppm 7.41 (m), 6.08 (m, 1H), 5.38(d, 1H, J= 17.2 Hz), 5.23(m, 2H)



2b

1-(4-Methylphenyl)-2-propen-1-ol

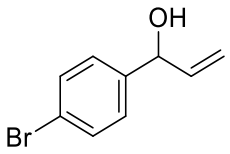
Analysis of a reaction mixture showed how the spectroscopic data agreed with that found in the literature (Lin, Liu & Wu, 2011). ^{1}H NMR (400 MHz, $CDCl_3$) δ in ppm 7.25 (d), 7.15 (d), 6.04 (m), 5.32 (d), 5.17 (m), 2.33 (s)



2c

1-(4-Methoxyphenyl)-2-propen-1-ol

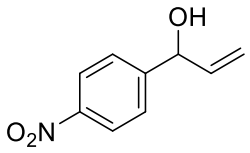
Analysis of a reaction mixture showed how the spectroscopic data agreed with that found in the literature (Lin, Liu & Wu, 2011). ^{1}H NMR (400 MHz, $CDCl_3$) δ in ppm 7.32 (d, 2 H, J=8.4 Hz), 6.91 (d, 2H, J=8.4 Hz), 6.07 (m, 1H), 5.33 (m), 5.20 (m), 3.79 (s)



2d

1-(4-Bromophenyl)-2-propen-1-ol

Analysis of a reaction mixture showed how the spectroscopic data agreed with that found in the literature (Lin, Liu & Wu, 2011). ^{1}H NMR (400 MHz, $CDCl_3$) δ in ppm 7.51 (d, 2H, J=8Hz), 7.28 (d, 2H, J=8 Hz), 6.03 (m, 1H), (d, 1H, J=16.8 Hz), 5.37 (d, 1H, J=10.4 Hz), 5.20 (bs, 1H)

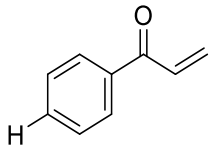


2e

1-(4-nitrophenyl)-2-propen-1-ol: Purification of the compound was accomplished using Yamazan smart flash chromatography with a Hexane:ethylacetate mixture. Spectroscopic data agreed with that found in the literature.(Kiloran et al, 2016) ^{1}H NMR (400 MHz, $CDCl_3$) δ in ppm 8.24 (d, 2H, J=8 Hz), 7.59 (d, 2H, J= 8 Hz), 6.011 (m, 1H), 5.37 (dd, 2H, J= 17 Hz, 10 Hz), 5.35 (m)

General Procedure for the Oxidation of a,b-unsaturated alcohols

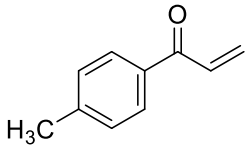
To an 25 mL roundbottom containing a stirbar was added (4.1 mmol, 1.6 equiv) PCC with (24.2 mmol, 6 equiv) $MgSO_4$ and maintained at room temperature. 2.57 mmol 1-(4-phenylderivative)-2-propen-1-ol. The reaction was monitored by TLC and the reaction quenched with (10 mL) diethyl ether after 15 minutes. The reaction stirred for 5 minutes prior to filtration through Florisil (2.461 g). The roundbottom washed three times with (15 mL) ether. The filtrate was concentrated under vacuum to give a crude oil.



3a

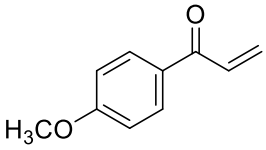
1-Phenyl-2-propen-1-one

Analysis of a reaction mixture showed how the spectroscopic data agreed with that found in the literature (Liu, Ji, Xu, Hu, Liu, Luo, & Guo, 2017). ^{1}H NMR (400 MHz, $CDCl_3$) δ in ppm 7.95 (d, 2H), 7.5 (d, 2H), 7.19 (dd, 1H, J_1=10.6 Hz, 17 Hz), 6.47 (d, 1H, J= 17.2 Hz), 5.97 (d, 1H, J= 10.4 Hz),



3b

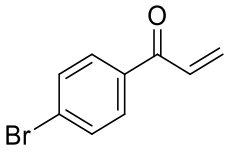
Analysis of a reaction mixture showed how the spectroscopic data agreed with that found in the literature (Liu et al., 2017). ^{1}H NMR (400 MHz, $CDCl_3$) δ in ppm 7.88 (d, 2H, J= 7.6 Hz), 7.30 (d, 2H, J= 7.6 Hz), 7.19 (dd, 1H, J_1=11.2 + 10.4 Hz, J_2= 17.2 Hz), 6.46 (d, 1H, J= 17.2 Hz), 5.93 (d, 1H, J= 10.4 Hz), 2.45 (s, 3H)



3c

1-(4'-Methoxyphenyl)-2-propen-1-one

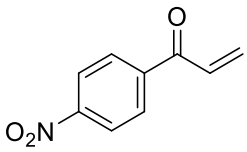
Analysis of a reaction mixture showed how the spectroscopic data agreed with that found in the literature (Liu et al., 2017). ^{1}H NMR (400 MHz, $CDCl_3$) δ in ppm 7.99 (d, 2H, J= 7.6 Hz), 6.99 (d, 2H, J= 8 Hz), 7.21 (dd, 1H, J_1=11.2 + 10.4 Hz, J_2= 17.2 Hz), 6.46 (d, 1H, J= 16.8 Hz), 5.90 (d, 1H, J= 10.4 Hz), 3.91 (s, 3H)



3d

1-(4-Bromophenyl)-2-propen-1-one

Analysis of a reaction mixture showed how the spectroscopic data agreed with that found in the literature (Liu et al., 2017). ^{1}H NMR (400 MHz, $CDCl_3$) δ in ppm 7.84(d, 2H, J= 7.6Hz), 7.65(d, 2H, J= 7.6 Hz), (dd, 1H, J_1=11.2 + 10.4 Hz, J_2= 17.2 Hz), 6.48 (d, 1H, J= 16.8 Hz), 5.97 (d, 1H, J= 10.8 Hz)

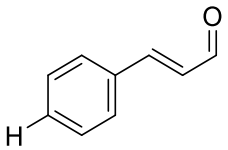


3e

1-(4-Nitrophenyl)-2-propen-1-one

Analysis of a reaction mixture showed how the spectroscopic data agreed with that found in the literature (Miyauchui, Hori, Hirai, Takebayashi, & Ibata, 1981). ^{1}H NMR (400 MHz, $CDCl_3$) δ in ppm 8.37 (d, 2H, J= 8 Hz), 8.10 (d, 2H, J= 8 Hz), (dd, 1H, J_1=10.6 Hz, J_2= 17 Hz), 6.52 (d, 1H, J= 17.2 Hz), 6.10 (d, 1H, J= 10.4 Hz)

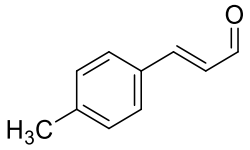
Carbonyl Transposition Product



4a

(2E)-3-Phenylprop-2-enal; Common name Cinnamaldehyde

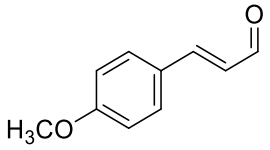
Analysis of a reaction mixture showed how the spectroscopic data agreed with that found in the literature (Kiloran et al., 2016). ^{1}H NMR (400 MHz, $CDCl_3$) δ in ppm 9.74 (d, 1H, J= 7.2 Hz), 7.59 (m, 2H), 7.51 (d, 1H)., 7.47 (m, 3H)



4b

(2E)-3-(4-methylPhenyl)prop-2-enal)

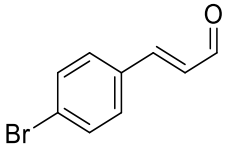
Analysis of a reaction mixture showed how the spectroscopic data agreed with that found in the literature (Kiloran et al., 2016). ^{1}H NMR (400 MHz, $CDCl_3$) δ in ppm 9.71 (d, 1H, J= 7.6 Hz), 7.49 (d, H, J=7.6 Hz) 7.45 (d, 1 H, J=9.2 Hz), 6.72 (dd, 1H, J=8 Hz, 15.6 Hz) 2.43 (s, 3H)



4c

(2E)-3-(4-methoxyPhenyl)prop-2-enal)

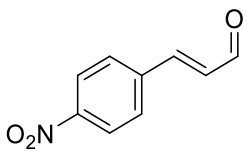
Analysis of a reaction mixture showed how the spectroscopic data agreed with that found in the literature (Kiloran et al., 2016). ^{1}H NMR (400 MHz, $CDCl_3$) δ in ppm 9.68 (d, 1H, J= 8 Hz), 7.56 (d, 2H, J=7.6 Hz) 7.45 (d, 1 H, J=16 Hz), 6.98 (d, 2 H, J=7.6 Hz), 6.64 (dd, 1H, J=8 Hz, 15.6 Hz) 3.89 (s, 3H)



4d

(2E)-3-(4-bromoPhenyl)prop-2-enal)

Spectroscopic data agreed with that found in the literature (Nordqvist, Bjőrkelid, Andaloussi, Jansson, Mowbray, Karlén, & Larhed, 2011) ^{1}H NMR (400 MHz, $CDCl_3$) δ in ppm 9.73 (d, 1H, J= 6.8 Hz), 7.5(m), 7.4(m), 6.65 (m)



4e

(2E)-3-(4-nitroPhenyl)prop-2-enal)

Analysis of a reaction mixture showed how the spectroscopic data agreed with that found in the literature (SigmaAldrich, CAS 49678-08-2). ^{1}H NMR (400 MHz, $CDCl_3$) δ in ppm 9.8 (d, 1H), 8.3 (d), 7.6 (d), 7.47(d) 6.75(dd, 1H)

APPENDIX B

ALTERNATIVE OXIDATION REACTIONS SPECTRA

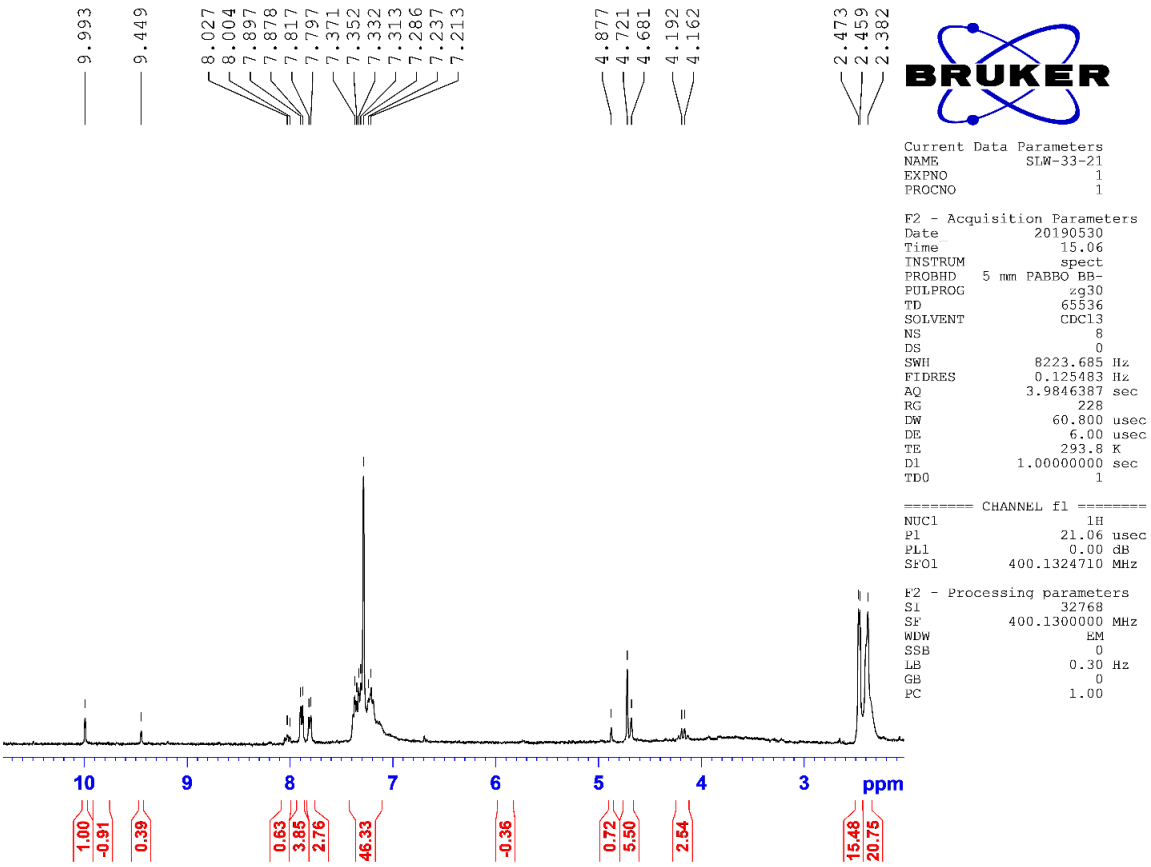


Figure A2.1 Oxidation of para methyl allyl alcohol

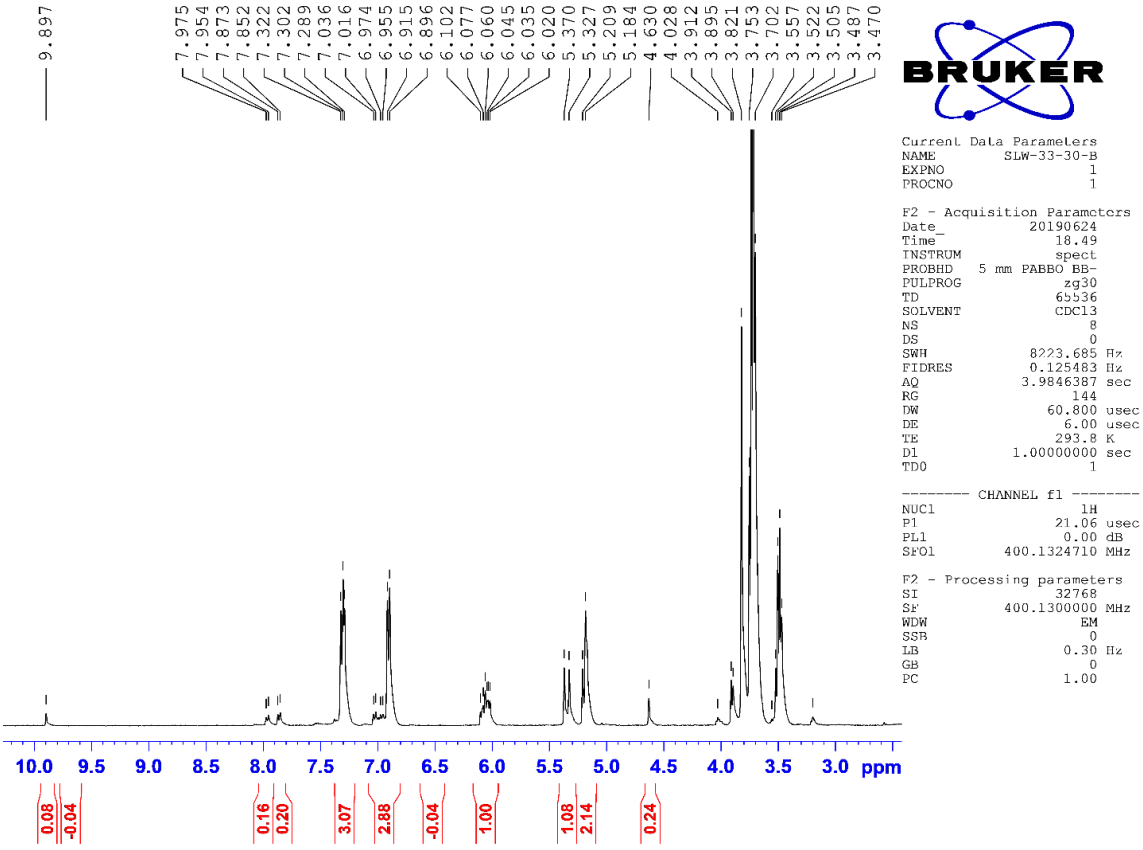


Figure A2.2 Oxidation of para methoxy allyl alcohol

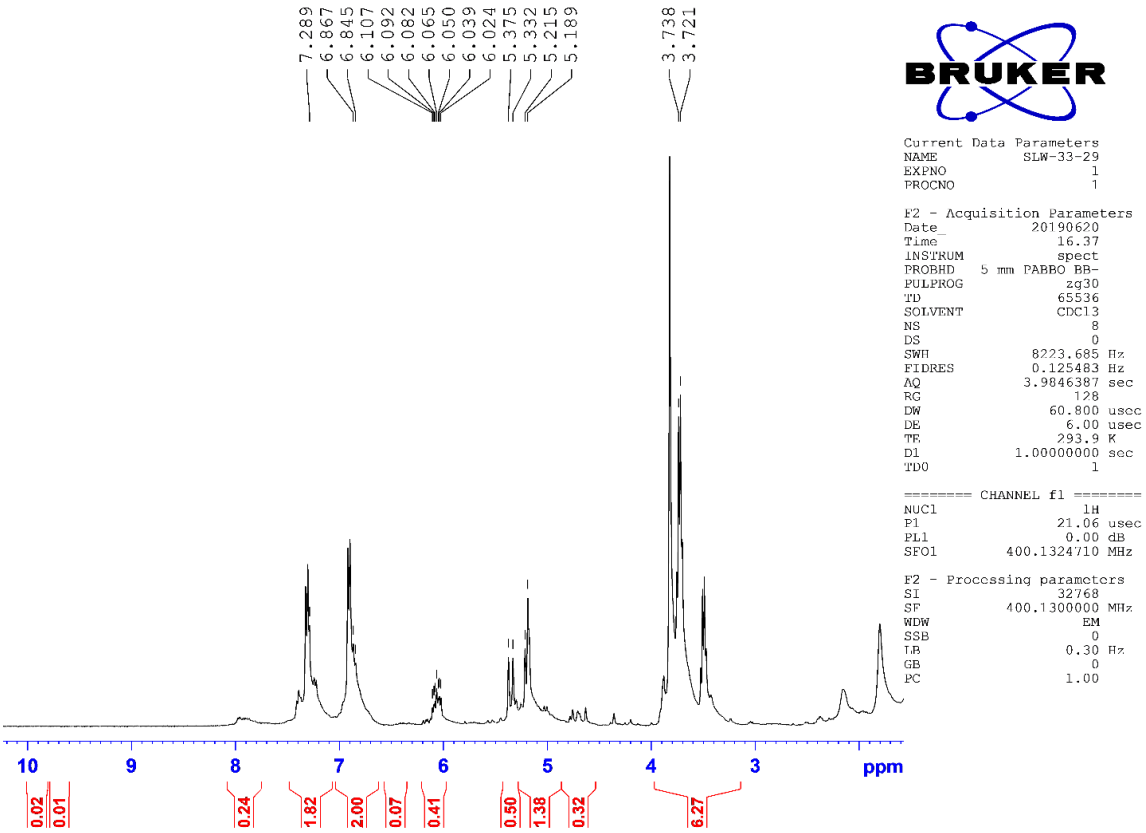


Figure A2.3: Oxidation of para methoxy benzylic allyl alcohol with the use of MnO_2 in chloroform.

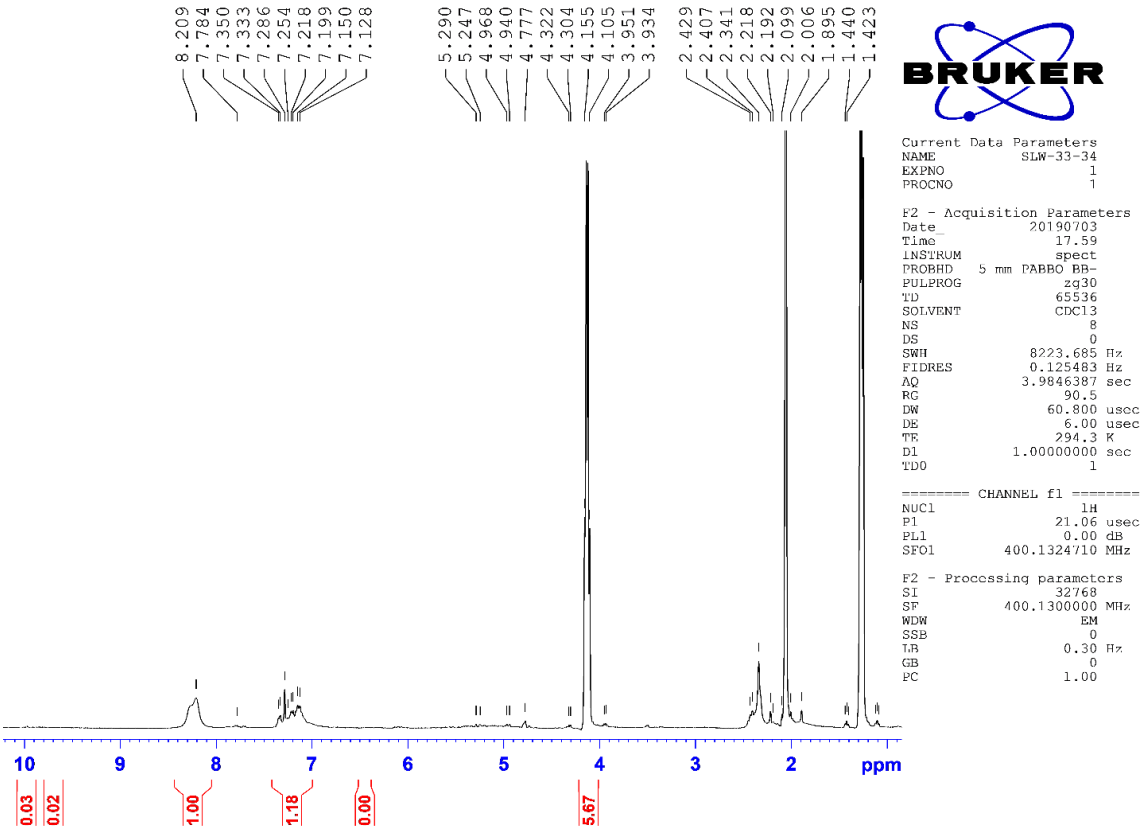


Figure A2.4: Oxidation using H_2O_2 and MnO_2 as a co-oxidant

Table A2.1

Time Oxidation of 2c to obtain (Figure 4.17)

	3c (%)	1c (%)	4c (%)	Conversion
0.000	55.8814	13.32648	30.79212	14.42306
5	55.51014	19.89447	24.5954	56.06117
10	40.08447	16.92633	42.98921	70.14252
15	46.03228	6.768181	47.19954	77.28116
20	50.77652	13.94014	35.28334	85.67207
60	44.548	9.108714	46.34328	85.11379
120	23.77193	53.3523	22.87577	97.33472